

Media Release

23 January 2017

Actelion announces results of the MAESTRO study with macitentan in patients with pulmonary arterial hypertension due to Eisenmenger Syndrome

ALLSCHWIL/BASEL, SWITZERLAND – 23 January 2017 – Actelion Ltd (SIX: ATLN) today announced that the MAESTRO study to assess the efficacy, safety and tolerability of macitentan in patients with pulmonary arterial hypertension (PAH) due to Eisenmenger Syndrome did not meet its primary objective.

Professor Nazzareno Galiè, Head of the Pulmonary Hypertension Center at the Institute of Cardiology, University of Bologna, and Steering Committee member for the MAESTRO study, commented: “The results of the MAESTRO study are very difficult to interpret. We have seen encouraging positive effects of macitentan in the response of N-terminal pro b-type natriuretic peptide plasma levels and hemodynamic measures. Although the results point towards a benefit of treatment with macitentan, we do not see a significant treatment effect on the primary endpoint of exercise capacity as measured in the 6 minute walk test. I believe this has been influenced by an unexpected improvement in the placebo arm of the study, which is unusual in a predominantly untreated PAH population. In fact, we have not seen such a persistent placebo effect in the multiple studies published so far in PAH. We need to fully analyze the data to understand what could have caused this phenomenon.”

In MAESTRO, 226 patients, including 135 patients in Functional Class II, were randomized in a 1:1 ratio to receive either 10 mg macitentan or placebo once daily. After 16 weeks of treatment, the mean change in 6-minute walk distance (6-MWD) from baseline was an increase of 18.3 meters (m) in the macitentan group and 19.7 m in the placebo group. The 6-MWD least-squares mean difference at Week 16 was -4.7 m between macitentan and placebo (95% CL: -22.8, 13.5 m; $p=0.612$, intention-to-treat (ITT)). There were 3 patients with missing 6-MWD values at Week 16 in the macitentan group, and imputation of zero meters at Week 16 was applied. In the per-protocol population (200 patients), the mean change in 6-MWD from baseline was an increase of 30.2 m in the macitentan group and 18.9 m in the placebo group. The 6-MWD least-squares mean difference at Week 16 was 6.4 m between macitentan and placebo (95% CL: -7.0, 19.8 m; $p=0.347$ per-protocol).

A 20% reduction of the exploratory biomarker endpoint, N-terminal pro b-type natriuretic peptide, an indicator of cardiac response, was observed after 16 weeks with macitentan

compared to placebo (95% CL: -32%, -6%; $p=0.006$) in the overall patient population. In addition, a 13% reduction in pulmonary vascular resistance index (PVRi) was observed after 16 weeks with macitentan compared to placebo (95% CL: -27%, 3%; $p=0.102$ ITT) in a hemodynamic sub-study of 39 patients (20 in the macitentan group and 19 in the placebo group). The mean change from baseline to Week 16 in PVRi was a decrease of -409.8 dyn.sec/cm⁵/m² in the macitentan group and an increase of 79.4 dyn.sec/cm⁵/m² in the placebo group. The PVRi least-squares mean difference at Week 16 was -434.8 dyn.sec/cm⁵/m² between macitentan and placebo (95% CL: -791.5, -78.0 m; $p=0.018$, ITT). Patients in the sub-study also showed an improvement in exercise capacity: the mean change in 6-MWD from baseline was an increase of 34.1 m in the macitentan group and 3.5 m in the placebo group. The 6-MWD least-squares mean difference at Week 16 was 24.9 m between macitentan and placebo (95% CL: -9.1, 59.0 m; $p=0.146$ ITT).

Guy Braunstein, Head of Global Clinical Development, commented: “We have seen encouraging results on multiple measures, particularly in the hemodynamic sub-study. Preliminary results from the open label extension of the study suggest that patients originally randomized to placebo and subsequently treated with macitentan showed an improvement in exercise capacity after 24 weeks. We must fully understand the results, in particular the reason for the large placebo effect, to know what might be changed so that we can deliver on our commitment to patients with Eisenmenger Syndrome.”

The MAESTRO safety set comprised 226 patients, 114 patients in the macitentan group and 112 patients in the placebo group. Macitentan was well tolerated in this patient population, and safety was, in general, consistent with the known safety profile for macitentan from previous clinical studies. The most frequently reported adverse events that occurred with higher frequency on macitentan vs. placebo were headache (11.4% vs. 4.5%) and upper respiratory tract infection (9.6% vs. 6.3%). Seven (6.1%) patients on macitentan experienced a serious adverse event compared with two (1.8%) patients on placebo. Two patients (1.8%) in each group discontinued the study treatment due to an adverse event. During the course of the study, there was one death reported (respiratory failure), in a patient receiving macitentan.

The company will now fully analyze the data and make them available through a peer-reviewed publication.

ABOUT EISENMENGER SYNDROME

Eisenmenger Syndrome represents the most advanced form of pulmonary arterial hypertension in conjunction with congenital heart disease (PAH-CHD). The congenital heart defect causes a shunt to develop between two chambers of the heart, so an increased blood flow returns to the lungs. The blood vessels in the lung arteries become stiff and narrow, resulting in pulmonary hypertension. Eisenmenger Syndrome occurs when the pressure in the pulmonary circulation becomes so great that the direction of

blood flow through the shunt reverses. It is associated with the development of chronic cyanosis and limited exercise capacity.

Patients with Down Syndrome represent between 25% and 50% of the Eisenmenger population, depending on cohort studied. To address the high unmet medical need for effective, targeted PAH therapies in this vulnerable population, Actelion extended the MAESTRO study with macitentan in Eisenmenger Syndrome patients to the Down Syndrome community. To ensure proper safeguards were established to protect the patients' rights and safety, the company worked with ethics committees, patient advocacy, support groups and patients' families.

ABOUT THE MAESTRO STUDY

MAESTRO (MAcitentan in Eisenmenger Syndrome To RestOre exercise capacity) was a Phase III multi-center, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the effects of macitentan on exercise capacity in patients with Eisenmenger Syndrome. The study was started in 2013 and global enrollment was completed in August 2016 with a total of 226 patients. Patients were randomized in a 1:1 ratio, with 114 patients in the macitentan 10 mg group and 112 patients in the placebo group over a 16-week treatment period. The study was conducted in 71 centers in 26 countries. The regions included North and Latin America, Europe, and Asia-Pacific. A sub-study was conducted in 8 countries and 11 centers to evaluate the effects of macitentan on hemodynamic parameters assessed by cardiac catheterization in patients with Eisenmenger Syndrome.

MAESTRO included 135 (59.7%) patients earlier in the course of the disease (Functional Class II) as well as 62 (27.4%) patients who received a PDE-5 inhibitor as background therapy. MAESTRO is one of the first randomized clinical trials in Eisenmenger to include patients with Down Syndrome. 20 (8.8%) patients with Down Syndrome were enrolled in the study, contributing to the broader advancement of knowledge and understanding of this disease.

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Notes to the Editor

ABOUT OPSUMIT® (MACITENTAN)

Opsumit (macitentan), an orally available endothelin receptor antagonist, resulted from a tailored drug discovery process in Actelion's laboratories.

In the US, Opsumit is indicated for the treatment of PAH, WHO Group I to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

In Europe, Opsumit is indicated, as monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

Opsumit is very likely to cause major birth defects. It is contraindicated for use in pregnancy. In the US, Opsumit is distributed under a risk evaluation and mitigation strategy.

AVAILABLE CLINICAL DATA

SERAPHIN, a global, pivotal Phase III study, was designed to evaluate the efficacy and safety of macitentan in patients with symptomatic PAH, through the primary endpoint of time to first morbidity and all-cause mortality event. A total of 742 patients were randomized to placebo (n=250), macitentan 3 mg (n=250), or macitentan 10 mg (n=242). The primary endpoint occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for macitentan 3 mg versus placebo was 0.70 (97.5% CI, 0.52 to 0.96; p=0.0108) and the hazard ratio for macitentan 10 mg versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; p<0.0001). Worsening of pulmonary arterial hypertension was the most frequent primary endpoint event. Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. The effect of macitentan on the endpoint was observed irrespective of background therapy for pulmonary arterial hypertension. The most commonly reported adverse drug reactions with Opsumit were nasopharyngitis (14.0%), headache (13.6%) and anemia (13.2%).

MERIT, a randomized controlled study, was designed to assess the efficacy and safety of macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). In MERIT, 80 inoperable patients were randomized to receive 10 mg of macitentan or placebo once daily over a 24 week treatment period. After 16 weeks the treatment effect was a significant 16% reduction in pulmonary vascular resistance (PVR) with macitentan compared with placebo (95% CL: -30%, -1%; p=0.04 intention-to-treat (ITT)). The efficacy observed was consistent across all sub-groups, including patients receiving background PH specific therapy at baseline (61%), including PDE-5 inhibitors (59%). Mean PVR decreased from baseline in both macitentan and placebo groups (geometric mean percent ratios of Week 16/baseline 73.0% and 87.2%, respectively). The study also showed a significant positive effect of macitentan compared to placebo on exercise capacity. After 24 weeks of treatment, the mean change in 6-minute walk distance (6-MWD) from baseline was an increase of 35 meters (m) in macitentan and 1 m in placebo. The 6-MWD least-squares mean difference at Week 24 was 34.0 meters between macitentan and placebo (95% CL: 2.9, 65.2 m; p=0.03). Macitentan was well tolerated in this patient population and safety was in general consistent with the known safety profile for macitentan from previous clinical studies. The most frequently reported adverse events that occurred with higher frequency on macitentan vs. placebo were peripheral edema (22.5% vs. 10.0%) and

events related to anemia (17.5% vs. 2.5%). Hemoglobin decreases were observed in both macitentan and placebo groups and in only one subject in each group hemoglobin values decreased below 100 g/L during the study.

Macitentan is currently being further evaluated in multiple studies to expanding the clinical utility of this important product in PAH and beyond.

ABOUT PULMONARY ARTERIAL HYPERTENSION (PAH)

PAH is a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual. The symptoms of PAH are non-specific and can range from mild breathlessness and fatigue during normal daily activity to symptoms of right heart failure and severe restrictions on exercise capacity and ultimately reduced life expectancy. PAH is one group within the classification of pulmonary hypertension (PH). This group includes idiopathic PAH, heritable PAH and PAH caused by factors which include connective tissue disease, HIV infection and congenital heart disease.

The last decade has seen significant advances in the understanding of the pathophysiology of PAH, which has been paralleled with developments of treatment guidelines and new therapies. Drugs targeting the three pathways that have been established in the pathogenesis of PAH are endothelin receptor antagonists (ERAs), prostacyclin receptor agonists, and phosphodiesterase-5 inhibitors. PAH treatments have transformed the prognosis for PAH patients from symptomatic improvements in exercise tolerance 10 years ago to delayed disease progression today. Improved disease awareness and evidence-based guidelines developed from randomized controlled clinical trial data have highlighted the need for early intervention, goal-oriented treatment and combination therapy. Learn more at <http://www.pahuman.com/>

Actelion Ltd.

Actelion Ltd. is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs.

Actelion is a leader in the field of pulmonary arterial hypertension (PAH). Our portfolio of PAH treatments covers the spectrum of disease, from WHO Functional Class (FC) II through to FC IV, with oral, inhaled and intravenous medications. Although not available in all countries, Actelion has treatments approved by health authorities for a number of specialist diseases including Type 1 Gaucher disease, Niemann-Pick type C disease, Digital Ulcers in patients suffering from systemic sclerosis, and mycosis fungoides type cutaneous T-cell lymphoma.

Founded in late 1997, with now over 2,500 dedicated professionals covering all key markets around the world including Europe, the US, Japan, China, Russia and Mexico, Actelion has its corporate headquarters in Allschwil / Basel, Switzerland.

Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SMI®). All trademarks are legally protected.

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