New macitentan (Opsumit) efficacy data in pulmonary arterial hypertension from SERAPHIN study presented at European Society of Cardiology Congress 2013

- Macitentan significantly reduced morbidity and mortality by 45% versus placebo
- Macitentan treatment provides sustained long-term improvements in exercise capacity
- No association found between changes in exercise capacity and long-term clinical outcomes
- Improved cardiopulmonary hemodynamics seen in macitentan-treated patients irrespective of baseline background pulmonary arterial hypertension (PAH) therapy or WHO functional class

ALLSCHWIL/BASEL, SWITZERLAND – 02 September, 2013 – Actelion (SIX: ATLN) today announced that new data for the investigational drug macitentan (Opsumit®) from the landmark SERAPHIN study was presented at the European Society of Cardiology Annual Congress 2013 in Amsterdam, the Netherlands. The presentations from leading experts in the field shared the latest findings on the impact of macitentan on exercise capacity, long term outcome and cardiopulmonary hemodynamics.

6MWD and long-term outcomes
In an oral presentation, Dr Nazzareno Galiè from the Institute of Cardiology, University of Bologna, Bologna, Italy presented data evaluating the association between 6MWD, a measure of exercise capacity and the long-term outcome measured with the endpoint of PAH-related death or hospitalization in the SERAPHIN study. Dr Galiè first shared that macitentan 10mg provided sustained long-term improvements in 6-minute walk distance (6MWD) versus placebo over 12 months (+25.4m, p<0.0001) and then discussed how 6MWD values at both baseline and month 6 were prognostic of long-term outcomes. Finally he showed data to demonstrate that changes in 6MWD from baseline to Month 6 were not associated with PAH-related death or hospitalization risk, raising important questions about the link between functional improvements and long term treatment success.

Dr Galiè commented about data presented at the ESC Congress 2013, “The SERAPHIN study is the first event-driven outcome trial in PAH to evaluate the association between 6MWD and long-term outcomes. These data confirm the efficacy of macitentan in improving the functional abilities of patients with PAH, as well as to significantly improve patient outcome.”
Dr Galiè added; “While our findings show that the absolute 6MWD value at baseline is prognostic, there is no clear relationship between the change in 6MWD from baseline and long-term treatment outcomes. The study results confirm that while the change in 6MWD is a useful marker of functional improvement, it is not an appropriate measure when looking to understand the impact of treatment on long-term morbidity and mortality. This observation reinforces the importance of selecting appropriate outcome measures when investigating new treatment options for our patients.”

**Hemodynamic effects of macitentan**

Further evidence of the efficacy of macitentan was provided in a second oral presentation, when Dr Adam Torbicki of the Department of Pulmonary Circulation and Thromboembolic Diseases, Center of Postgraduate Medical Education, ECZ-Otwock, Poland, discussed the results of a substudy of SERAPHIN that investigated the impact of macitentan on cardiopulmonary hemodynamics in pulmonary arterial hypertension.

Dr Torbicki commented; “Macitentan significantly improved hemodynamic parameters overall in PAH patients in the SERAPHIN study. Furthermore, in our substudy, consistent improvements in pulmonary vascular resistance (PVR) and cardiac index (CI) were achieved with macitentan irrespective of background PAH therapy or baseline WHO functional class.”

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion also commented; “We are delighted that once again the findings of the SERAPHIN study have confirmed the efficacy of macitentan in making clinically relevant changes to cardiopulmonary hemodynamics and easing the burden of patients with PAH. Dr Galiè’s confirmation that the change in 6MWD results are not linked to relevant long-term outcomes in PAH reinforces the importance of the innovative approach taken in SERAPHIN. The true efficacy of long-term treatments should be established through the investigation of morbidity and mortality, because of what matters most to our patients and physicians: reduce the progression of PAH.”

### NOTES TO THE EDITOR

**Oral Presentations at ESC Congress 2013**

**Sustained effect of macitentan, a novel oral endothelin receptor antagonist, on exercise capacity and the association of its measure with long-term outcomes in pulmonary arterial hypertension.**

N Galiè, R Channick, M Delcroix, H-A Ghofrani, P Jansa, F-O Le Brun, G Simmoneau, LJ Rubin
Oral abstract presentation: September 01, 11.00–11.15
Abstract Number: 1061

**Effect of macitentan on haemodynamics in patients with pulmonary arterial hypertension: results from the long-term, randomised, placebo-controlled SERAPHIN trial**

A Torbicki, S Mehta, L Perchenet, T Pulido, BKS Sastry, O Sitbon, R Souza, LJ Rubin, G Simmoneau
Oral abstract presentation: September 01, 11.15–11.30
Abstract Number: 1062

- New macitentan data from SERAPHIN study at ESC 2013.-
ABOUT THE SERAPHIN STUDY

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) was the largest and longest randomized, controlled study in PAH patients to include a clearly defined morbidity/mortality primary endpoint [2]. The pivotal Phase III study was designed to evaluate the efficacy and safety of macitentan (Opsumit®) - a novel dual endothelin receptor antagonist that resulted from a tailored drug discovery process - through the primary endpoint of time to first morbidity and all-cause mortality event in patients with symptomatic PAH.

Global enrollment was completed in December 2009 with a total of 742 patients. Patients were randomized 1:1:1 to receive two different doses of macitentan (3 mg and 10 mg once daily) or placebo. Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. This event-driven study was conducted in 151 centers from almost 40 countries in North America, Latin America, Europe, Asia-Pacific and Africa and was completed in the first half of 2012, with 287 patients having an adjudicated event.

ABOUT SERAPHIN STUDY DATA

Patients were randomized to placebo (n=250), macitentan 3 mg (n=250), or macitentan 10 mg (n=242). The primary end point 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 end point event. The effect of macitentan on this end point was observed irrespective of background therapy for pulmonary arterial hypertension. [1]

ABOUT THE SAFETY AND TOLERABILITY PROFILE

Macitentan was well tolerated in the SERAPHIN study. The overall incidence of adverse events reported and treatment discontinuations due to adverse events in patients was similar across all groups. The incidence of serious adverse events was lower in patients treated with macitentan compared to placebo, with 52% and 45% of patients in the macitentan 3 mg and 10 mg groups respectively, and 55% of patients in the placebo group experiencing serious adverse events.

Compared with placebo, a higher proportion of macitentan-treated patients had nasopharyngitis, headache, and anemia. One patient in each treatment group discontinued due to anemia.

Elevations of liver alanine or aspartate aminotransferases greater than three times the upper limit of normal were observed in 4.5 percent of patients receiving placebo, 3.4 percent of patients on 10 mg of macitentan and in 3.6 percent of patients on 3 mg of macitentan. In addition, no difference in fluid retention (edema) was observed between macitentan and placebo). [1]

ABOUT MACITENTAN (OPSUMIT®)

Macitentan (Opsumit®) is a novel dual endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process with the target of developing an ERA optimized for efficacy and safety [3]. Macitentan has a number of potentially key beneficial characteristics including increased in vivo preclinical efficacy versus existing ERAs resulting from sustained receptor binding [4] and physicochemical properties that allow enhanced tissue penetration [5]. The clinical pharmacology program also indicated a low propensity of macitentan for drug-drug interactions [6,7,8].

- New macitentan data from SERAPHIN study at ESC 2013.-
ABOUT MACITENTAN (OPSUMIT®) SUBMISSIONS TO HEALTHCARE AUTHORITIES

On 22nd October 2012 Actelion announced that it had submitted a new drug application to the US Food and Drug Administration (FDA) seeking approval for macitentan (Opsumit®) in patients with pulmonary arterial hypertension.

On 22nd November 2012 Actelion announced that it had successfully submitted the Market Authorisation Application to the European Medicines Agency (EMA) and a validation letter had been received.

Regulatory review is also ongoing in Canada, Switzerland, Australia, Taiwan and Mexico.

ABOUT PULMONARY ARTERIAL HYPERTENSION [9, 10]

Pulmonary arterial hypertension (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), prostacyclins 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.

Despite these advances in PAH, survival rates are unacceptably low and PAH remains incurable.

References

2. For a general discussion of a clinically meaningful outcome end-point, please see: Proceedings of the 4th world symposium on pulmonary hypertension. J Am Coll Cardiol 2009;54(1 Suppl).

- New macitentan data from SERAPHIN study at ESC 2013.


Actelion Ltd

Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion’s first drug Tracleer® (bosentan), an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union, Japan, Canada, Australia and Switzerland. Actelion, founded in late 1997, is a leading player in innovative science related to the endothelium - the single layer of cells separating every blood vessel from the blood stream. Actelion’s over 2,300 employees focus on the discovery, development and marketing of innovative drugs for significant unmet medical needs. Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SM®).

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