Media Release

10 September 2013

Macitentan (Opsumit) morbidity and mortality data in pulmonary arterial hypertension from SERAPHIN study presented at European Respiratory Society Congress 2013.

- Macitentan significantly reduced the risk of morbidity and mortality by 45% versus placebo
- Macitentan reduced the risk of PAH-related death or hospitalization by 50%

ALLSCHWIL/BASEL, SWITZERLAND – 10 September, 2013 – Actelion (SIX:ATLN) today announced that key morbidity and mortality data from the landmark SERAPHIN study was shared during an oral presentation at the European Respiratory Society Annual Congress 2013 in Barcelona, Spain. The presentation highlighted that the investigational drug macitentan (Opsumit®) from Actelion significantly reduced the risk of morbidity and mortality events in patients with pulmonary arterial hypertension (PAH).

The presentation from Professor Hossein-Ardeschir Ghofrani of the University Hospital Giessen, Giessen, Germany, focused on key efficacy data for macitentan from the recent landmark SERAPHIN trial.

Professor Ghofrani presented data showing the primary endpoint of the study, time from treatment initiation to first morbidity or mortality event. Initially he showed the results of a 45% reduction in the risk of morbidity/mortality events for macitentan 10mg versus placebo (p<0.0001) in the 742 patients taking part in the largest ever trial in PAH. Professor Ghofrani then went on to note that the effect seen early in the study, was sustained throughout the study and was observed regardless of baseline WHO functional class or background PAH therapy.

The SERAPHIN study also demonstrated a significant treatment effect for macitentan 10mg in its secondary outcome measures and 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. Professor Ghofrani presented data showing that the reduction in risk of hospitalization for PAH and death due to PAH associated with macitentan 10mg treatment versus placebo was 50% (p<0.0001) and that all-cause mortality was reduced by 36% (p=ns).

Professor Ghofrani commented on the findings shared at ERS; “As the first event-driven, outcomes trial in PAH, the findings of the SERAPHIN study have been keenly anticipated. Last month saw the publication of the SERAPHIN morbidity and mortality data in The New England Journal of Medicine. At ERS I have highlighted the hospitalization data in more details and shown that
macitentan significantly reduced the risk of death due to PAH and hospitalizations for PAH. These data are impressive and give real hope for the patients and all those involved in PAH management."

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion added: "The data presented at ERS demonstrate once again Actelion’s ongoing commitment to developing novel, effective treatments for PAH and to sharing robust data from our clinical trial program with the medical community. Just days ago the primary paper of our landmark SERAPHIN study appeared in The New England Journal of Medicine, and in the last 12 months key data have been presented at CHEST, ATS, ESC and ERS. Actelion is continuing to work with regulatory authorities worldwide to bring this important medicine to patients. The next 12 months promise to be equally important, with publication of newdata from the SERAPHIN study and feedback expected from a number of health authorities. For Actelion, macitentan (Opsumit®) is a key part of our future that we believe will allow us to sustain and grow our pulmonary arterial hypertension business and deliver new hope to the PAH community."

###

NOTES TO THE EDITOR

ORAL PRESENTATION AT ERS Congress 2013

Effect of macitentan on morbidity and mortality in pulmonary arterial hypertension: a randomised controlled trial


Oral presentation: September 09, 10.00–10.15

Abstract reference: TBC

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

- New macitentan data from SERAPHIN study at ERS 2013.
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 physiochemical 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].

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.

- New macitentan data from SERAPHIN study at ERS 2013.-
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 CollCardiol 2009;54(1 Suppl).

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 SMI®).
For further information please contact:

Roland Haefeli
Senior Vice President, Head of Investor Relations & Public Affairs
Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil
+41 61 565 62 62
+1 650 624 69 36
www.actelion.com

The above information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company's investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company's existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.