Further positive Opsumit (macitentan) data in pulmonary arterial hypertension presented at CHEST 2013

ALLSCHWIL/BASEL, SWITZERLAND – 29 October 2013 – Actelion (SIX: ATLN) today announced that following the recent FDA approval and positive CHMP opinion for macitentan (Opsumit®) in pulmonary arterial hypertension (PAH), further positive data on the efficacy of macitentan from the SERAPHIN study were presented at CHEST 2013 in Chicago, USA (26–31 October 2013).

Professor Gérald Simonneau of Hôpital Universitaire de Bicêtre, Le Kremlin-Bicêtre, France gave an oral presentation of data from a subgroup analysis of SERAPHIN revealing that treatment-naïve patients receiving macitentan 10mg had significantly improved long-term outcomes, irrespective of the time from diagnosis to treatment initiation.

Macitentan 10mg reduced the risk of morbidity/mortality by 60% in ‘incident’ patients compared to placebo (hazard ratio 0.40, 95% CL 0.20–0.73), in ‘prevalent’ patients, macitentan 10mg reduced the risk of morbidity/mortality by 53% (hazard ratio 0.47, 95% CL 0.24–0.91). The risk reductions for the secondary endpoint of death due to PAH or hospitalization for PAH (DHPAH) were 77% (hazard ratio 0.23, 95% CL 0.09–0.57) and 62% (hazard ratio 0.38, 95% CL 0.16–0.92) for incident and prevalent patients treated with macitentan 10mg versus placebo, respectively.

Incident cases are those that were diagnosed shortly before entering the study (median time post diagnosis to study inclusion of 50 days). Prevalent cases are those whose disease was diagnosed more than 6 months prior entering in the study (median time from diagnosis to study inclusion 834 days). In SERAPHIN, the incident patient group had a worse prognosis than the prevalent group however, despite this, both groups receiving macitentan saw a significant improvement in the risk of morbidity/mortality events.

The most common adverse reactions (more frequent than placebo by 3% or more) observed in patients treated with Opsumit were anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection.

Professor Simonneau commented, “These data are important as they demonstrate that macitentan is an effective first-line therapy for both newly diagnosed patients and those who have waited longer before starting treatment. Despite having a poorer prognosis, incident patients benefit as much as
prevalent patients when treated with macitentan in SERAPHIN. This is very encouraging news for all of our treatment-naïve patients and supports earlier diagnosis and treatment for improved outcomes in PAH today.”

CHEST 2013 also saw additional SERAPHIN data from an oral presentation by Professor Rogério Souza of the University of São Paulo, São Paulo, Brazil entitled ‘Association between WHO functional class and long-term prognosis in patients with pulmonary arterial hypertension: Data from SERAPHIN, a randomized controlled study of macitentan’. Professor Souza’s presentation demonstrated that worsening functional class is related to worse long-term clinical outcomes, while improving functional class is associated with better long-term clinical outcomes. He noted that this underlines the importance of maintaining or improving functional class where possible to improve the prognosis for PAH patients.

Further SERAPHIN data will also be presented at the meeting in a poster presentation by Dr Richard Channick of Massachusetts General Hospital, Boston, USA entitled ‘Do parameters of cardiac function predict long-term outcomes in patients with pulmonary arterial hypertension? Data from SERAPHIN, a randomized controlled study of macitentan.’

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion commented, “Following on from the recent US FDA approval and positive CHMP opinion these data from the long-term SERAPHIN study reinforces that Opsumit 10 mg can delay disease progression in PAH patients over the long-term. With this data, specific to incident and prevalent patients, we are truly seeing the benefits to the PAH community of undertaking the largest and longest trial ever in PAH, and in focusing on the most clinically relevant endpoints of morbidity and mortality.”

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NOTES TO THE EDITOR

ORAL PRESENTATIONS AT CHEST 2013


Oral presentation: October 28, 13.45-15.15

Association between WHO functional class and long-term prognosis in patients with pulmonary arterial hypertension: Data from SERAPHIN, a randomized controlled study of macitentan.

Oral presentation: October 28, 13.45-15.15
POSTER PRESENTATIONS AT CHEST 2013

Do parameters of cardiac function predict long-term outcomes in patients with pulmonary arterial hypertension? Data from SERAPHIN, a randomized controlled study of macitentan.

Poster presentation: October 30, 13.30-14.30

ABOUT OPSUMIT® (MACITENTAN)

Opsumit® (macitentan) is a novel dual endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process with the target of developing an ERA to address efficacy and safety [1].

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 Opsumit® (macitentan) - 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 enrolment 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. [3]

ABOUT THE SAFETY AND TOLERABILITY PROFILE

Opsumit is contraindicated in pregnancy because it may harm the developing fetus. Females of reproductive potential should be counselled on the use of reliable contraception and have a negative pregnancy test prior to initiating therapy and monthly thereafter.

The US label for Opsumit® carries a Boxed Warning alerting patients and health care professionals that the drug should not be used in pregnant women. Female patients can receive the drug only through the Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program.

Other ERAs have been associated with elevations of aminotransferases, hepatotoxicity, and liver failure. Liver enzyme tests should be obtained prior to initiation of Opsumit® and repeated during treatment as clinically indicated. If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by clinical symptoms of hepatotoxicity, discontinue Opsumit®.
Decreases in hemoglobin concentration and hematocrit occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. The decreases occurred early and stabilized thereafter. Decreases in hemoglobin seldom require transfusion. Initiation of Opsumit® is not recommended in patients with severe anemia. Hemoglobin should be measured prior to initiation of treatment and repeat during treatment as clinically indicated.

The most common adverse reactions observed in patients treated with Opsumit were anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection.

ABOUT OPSUMIT® (MACITENTAN) SUBMISSIONS TO HEALTHCARE AUTHORITIES

Approval of the new drug application for Opsumit® (macitentan) was issued by the US Food and Drug Administration (FDA) on 18 October 2013 for the treatment of pulmonary arterial hypertension (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.

On October 25, 2013, the CHMP recommended that the European Commission approve Opsumit®, as monotherapy or in combination, for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class II to III. Regulatory reviews are ongoing in Canada, Switzerland, Australia, Taiwan, Korea and Mexico.

ABOUT PULMONARY ARTERIAL HYPERTENSION [4, 5]

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.

In PAH, survival rates are unacceptably low and PAH remains incurable.

References

(ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537

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®).

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- Opsumit data in PAH presented at CHEST 2013 -