Media Release

07 November 2016

Actelion announces positive results of the MERIT study with macitentan in patients with chronic thromboembolic pulmonary hypertension

Actelion will host an investor conference call and webcast to discuss the MERIT results and provide an update on its cardiovascular pipeline at 14:00 hrs CET

ALLSCHWIL/BASEL, SWITZERLAND – 07 November 2016 – Actelion Ltd (SIX: ATLN) today announced that the MERIT study to assess the efficacy, safety and tolerability of macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH; Pulmonary hypertension group 4) has met its primary endpoint.

In MERIT, 80 inoperable CTEPH patients were randomized 1:1 to receive either macitentan 10 mg once daily or placebo. 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, included 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).

Guy Braunstein, Head of Global Clinical Development at Actelion, commented: “Inoperable chronic thromboembolic pulmonary hypertension is associated with a poor prognosis if left untreated, and additional therapeutic options are needed for these patients who are not candidates for surgery. I am very pleased that the study has shown a significant decrease in PVR with macitentan and by the significant improvement in exercise capacity. I would like to thank everyone who has participated in this study. The company will now fully analyze the data and discuss the findings with health authorities.”

The MERIT safety set comprised 80 patients, who received at least one dose of study treatment, 40 patients in each macitentan and placebo groups. All 40 patients in the

macitentan group and 34 patients in the placebo group completed the protocol-defined treatment period of 24 weeks. 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. Three (7.5%) patients on macitentan experienced a serious adverse event compared with seven (17.5%) patients on placebo. No elevations of liver aminotransferases greater than three times the upper limit of normal were observed in the study. All treatment discontinuations occurred in the placebo group. During the course of the study, there were two deaths reported, both in patients receiving placebo.

Full data from this study will be made available through scientific disclosure at an upcoming congress and peer-reviewed publication.

ABOUT CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

CTEPH is a unique form of pulmonary hypertension caused by chronic obstruction of the pulmonary arteries. The obstructions can result from blood clots that become stuck to the walls of the pulmonary arteries. The lining of the pulmonary arteries then begins to form excess tissue around the clots, transforming them into fibrous scar tissue that is attached to the artery wall. This creates a blockage that restricts the blood flow and increases the blood pressure, causing pulmonary hypertension and chronic stress to the right side of the heart – the heart risks going into failure over time.

Pulmonary thromboendarterectomy (PTE) remains the preferred treatment for CTEPH. However, certain CTEPH patients are not operative candidates due to the nature of the disease, location of the thrombi or multiple co-morbid conditions. New medical treatment options are therefore needed for the effective management of this patient group.

###

Notes to the Editor

ABOUT THE MERIT STUDY

MERIT (Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension) was a Phase II prospective, randomized, placebo-controlled, double-blind, multi-center, parallel-group study to assess the efficacy, safety and tolerability of 10 mg macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

In MERIT, 80 inoperable patients were randomized in a 1:1 ratio into 2 treatment groups (macitentan 10 mg or placebo) over a 24 week treatment period. The study started in August 2014 and was completed in September

2016. Patients with symptomatic PH in WHO Functional Class (FC) III or IV at baseline were allowed to receive PH background therapy throughout the study, including PDE-5 inhibitors or oral/inhaled prostanoids. All patients included into the study underwent independent operability assessment based on local or central adjudication committees.

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, included 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.

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%).

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/

References

1. Marius M. Hoeper. Pharmacological therapy for patients with chronic thromboembolic pulmonary hypertension. European Respiratory Review 2015 24: 272-282
2. Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT).Eur Heart J. 2016 Jan 1;37(1):67-119.
3. Gatzoulis MA, Beghetti M, Landzberg MJ, Galiè N. Pulmonary arterial hypertension associated with congenital heart disease: recent advances and future directions. Int J Cardiol 2014;177:340-7.
4. Pulido T et al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. N Engl J Med 2013;369:809-18.
5. Simonneau G, et al. Incident and prevalent cohorts with pulmonary arterial hypertension: insight from SERAPHIN. Eur Respir J. 2015;46:1711-20
6. Channick RN, et al. Effect of macitentan on hospitalizations: results from the SERAPHIN trial. *JACC Heart Fail*. 2015;3:1-8
7. Youssef P, et al. Vachiery JL, Adir Y, Barbera JA et al. Pulmonary hypertension due to left heart diseases. Journal of the American College of Cardiology 2013;62:D100-8.
8. Proceedings of the 5th world symposium on pulmonary hypertension J Am Coll Cardiol. 2013;62(Suppl)

INVESTOR CONFERENCE CALL / WEBCAST

Date/Time

07 November 2016	14:00 hrs - 15:00 hrs	Basel
	13:00 hrs - 14:00 hrs	London
	08:00 hrs - 09:00 hrs	New York

Conference Call Connect #: Dial-in participants should start calling the number below 10-15 minutes before the conference is due to start.

Dial:	Europe:	+41 (0)44 583 18 01
	UK:	+44 (0)203 009 24 60
	US:	+1 855 228 38 74

Participant's mode: Listen-Only with possibility to open individual lines during Q&A session. Participants will be asked for their name and company.

Webcast Access: Webcast participants should go to the Actelion website http://www.actelion.com 10-15 minutes before the conference is due to start.

Webcast Replay: The archived Investor Webcast will be available for replay through http://www.actelion.com/ approximately 60 minutes after the call has ended.

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.

For further information please contact:
Andrew Weiss
Senior Vice President, Head of Investor Relations & Corporate Communications
Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil
+41 61 565 62 62
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.