Selexipag meets primary endpoint in pivotal Phase III GRIPHON outcome study in patients with pulmonary arterial hypertension

ALLSCHWIL, SWITZERLAND – 16 June 2014 – Actelion Ltd (SIX: ATLN) today announced the top-line results of the pivotal Phase III GRIPHON study in 1,156 patients with pulmonary arterial hypertension (PAH) with selexipag, the first selective oral prostacyclin IP receptor agonist. Initial analysis shows that the event-driven outcome study has met its primary efficacy endpoint with high statistical significance. Selexipag decreased the risk of a morbidity/mortality event versus placebo by 39% (p<0.0001). Efficacy observed was consistent across the key subgroups; age, gender, WHO Functional Class, PAH etiology and background PAH therapy. Patients were treated for up to 4.3 years. The overall tolerability profile of selexipag in GRIPHON was consistent with prostacyclin therapies.

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion commented: “I am overwhelmed by the result of this long-term outcome study that evaluated selexipag in a setting where 80 percent of patients already received oral PAH therapy at baseline. Together with our partner Nippon Shinyaku, we are now one step closer to bringing an effective oral therapy targeting the prostacyclin pathway to the PAH community. We will now work diligently to complete the analyses with the goal to initiate first regulatory filings with Health Authorities as soon as possible.”

Gérald Simonneau, M.D., Professor of Pulmonology and Head of the Department of Pulmonary Disease and Intensive Care Unit, Université Paris-Sud, Le Kremlin-Bicêtre, France and Steering Committee member commented: “I have been prescribing intravenous prostacyclin therapies in PAH patients for almost twenty years. Today’s GRIPHON results represent a major step forward. For the first time, with selexipag, we have an oral compound acting on the prostacyclin pathway showing a significant risk reduction on a highly clinically relevant endpoint.”
Guy Braunstein, M.D. and Head of Global Clinical Development commented: “I would like to thank the PAH community for their long-term commitment, which made this, the second morbidity/mortality outcome study from Actelion possible. While we are just beginning to analyze the data, the top-line results we have in hand today are already impressive. The concept of individualized uptitration of selexipag according to tolerability was successful, with a consistent result seen across the entire dose range.”

Vallerie McLaughlin M.D., Director of the Pulmonary Hypertension Program in the Division of Cardiovascular Medicine at the University of Michigan, United States and Steering Committee member commented: “The GRIPHON study results hold the promise that selexipag might open up the prostacyclin pathway to different groups of patients given the consistent efficacy findings across key subgroups evaluated in this long-term outcome study. In addition, GRIPHON has shown once again that registration studies that follow the robust morbidity/mortality definitions - as recommended by the 4th and 5th World symposia on Pulmonary Hypertension - have the potential to deliver truly meaningful clinical information.”

Detailed study results will be made available through scientific disclosure at upcoming congresses and in peer reviewed publications.

DOISING IN GRIPHON
Uptitration of selexipag allows each patient's maintenance dose to be individualized based on tolerability. Dosing in GRIPHON was initiated at 200 micrograms (mcg) bid and increased in steps of 200 mcg twice daily up to a maximum of 1600 mcg twice daily.

ABOUT THE SAFETY AND TOLERABILITY IN GRIPHON
The most common adverse events in GRIPHON that occurred with higher frequency on selexipag than placebo were in-line with those known in prostacyclin therapies; headache, diarrhea, nausea, jaw pain, vomiting, pain in extremity, myalgia, nasopharyngitis and flushing.

The proportion of patients discontinuing treatment due to adverse events was 14 percent on selexipag and 7 percent on placebo.

ABOUT GRIPHON
GRIPHON, (Prostacyclin (PGI2) Receptor agonist In Pulmonary arterial Hypertension) was a randomized, multicenter, double-blind, placebo-controlled trial evaluating the long-term efficacy and safety of oral selexipag in patients with pulmonary arterial hypertension.

The GRIPHON study was the largest outcome trial ever conducted in PAH, enrolling patients in 181 centers from 39 countries in North and Latin America, Europe, Asia-Pacific and Africa.
GRIPHON enrollment was completed in May 2013 with 1’156 patients and represents the largest randomized, controlled study in PAH patients. Patients received twice daily administration of selexipag or placebo and were also permitted to receive background therapy of endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor when on a stable dose for at least 3 months prior to enrollment. At baseline, 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two.

This pivotal, event-driven study was designed to demonstrate a prolongation of time to the first morbidity/mortality event for selexipag compared to placebo and to evaluate the safety of the selexipag in PAH patients. All morbidity and mortality events reported by the investigators were adjudicated by an independent Critical Event Committee blinded to the study treatment.

ABOUT SELEXIPAG

Selexipag, originally discovered and synthesized by Nippon Shinyaku, is a potent, orally available, selective prostacyclin IP receptor agonist.

Selexipag selectively targets the prostacyclin receptor (also called IP-receptor). The IP receptor is one of 5 types of prostanooid receptor. Prostacyclin activates the IP receptor inducing vasodilation and inhibiting proliferation of vascular smooth muscle cells. Selexipag, unlike prostacyclin analogs, is selective for the IP receptor over other prostanooid receptors. In preclinical models selective IP receptor agonism has shown to maintain efficacy and reduce the risk of side effects mediated by activation of other prostanooid receptors, such as EP₁ and EP₃ receptors. [2,4,5]

Selexipag was previously evaluated in a Phase II, 43-patient, placebo-controlled, double-blind study, where patients were randomized in a 3:1 ratio receiving selexipag or placebo on top of PDE-5 inhibitor and/or ERA [6]

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Notes to Editor:

PULMONARY ARTERIAL HYPERTENSION (PAH)

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), prostacyclin analogs 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.

ABOUT PROSTACYCLIN
Prostacyclin is a prostanoid and serves as a signaling molecule in the human body. It is produced, like other vasoactive substances, by endothelial cells. Prostacyclin induces vasodilation, is anti-proliferative, has anti-inflammatory effects and inhibits platelet aggregation. In certain disease conditions, the production of prostacyclin by the endothelium is impaired, allowing for example the deleterious effects of excessive levels of endothelin to predominate.

ABOUT THE ACTELION / NIPPON SHINYAKU ALLIANCE
Actelion and Nippon Shinyaku entered into an exclusive worldwide alliance in April 2008 to collaborate on selexipag, a first orally-available, selective prostacyclin IP receptor agonist for patients suffering from pulmonary arterial hypertension (PAH). This compound was originally discovered and synthesized by Nippon Shinyaku. Actelion is responsible for global development and commercialization of selexipag outside Japan, while the two companies will co-develop and co-commercialize in Japan. Nippon Shinyaku will receive milestone payments based on development stage and sales milestones as well as royalties on any sales of selexipag.

References

Dr. McLaughlin is a consultant to Actelion

- Actelion announces results of the GRIPHON study with selexipag -
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 2,400 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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