



## Media Release

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17 May 2010

### **Actelion announces presentation of positive Phase II results with selexipag in patients with pulmonary arterial hypertension at the American Thoracic Society 2010 International Conference**

**ALLSCHWIL, SWITZERLAND – 17 May 2010** – Actelion Ltd (SIX: ATLN) announced today that full data from the Phase II study of selexipag (proposed INN), the company's first-in-class, orally available, selective IP receptor agonist in patients with pulmonary arterial hypertension (PAH) were presented by Gerald Simonneau M.D., Ph.D, Chief of the Department of Pneumology, Hospital Antoine Bécclère, Clamart, France, and Lead investigator on the trial, during the American Thoracic Society's (ATS) 2010 international conference taking place this week in New Orleans.

Results of the 43-patient, placebo-controlled, double-blind study, where patients were randomized in a 3:1 ratio receiving selexipag or placebo, showed a statistically significant reduction in pulmonary vascular resistance (PVR; primary parameter for the study). The treatment effect was shown to be 30.3 percent after 17 weeks of treatment ( $p=0.0045$ ). Results also showed an encouraging numerical improvement in 6-minute walk distance (6MWD), which was a secondary endpoint of this trial. Selexipag was well tolerated and the safety profile was in-line with the expected pharmacologic effect.

Prof. Simonneau M.D., Ph.D. commented: "These Phase II results are very encouraging, particularly considering that the efficacy observed, is on top of oral background therapy. They strongly support the study of this very promising oral IP receptor agonist in the ongoing Phase III study."

Treatment with selexipag was initiated at 200 microgram (mcg) b.i.d., which, if tolerated, was uptitrated to b.i.d. 400, 600 and 800 mcg on Days 3, 7 and 21, respectively. All patients enrolled in the trial were on background therapy with endothelin receptor antagonists and/or phosphodiesterase type 5 inhibitors before and during the course of the study. The primary efficacy endpoint of the trial was change from baseline to Week 17 in PVR. The secondary endpoints included 6MWD and other hemodynamic parameters. Safety and tolerability were evaluated in all enrolled patients.

Selexipag is currently being evaluated in the Phase III GRIPHON, (Prostacyclin (PGI<sub>2</sub>) Receptor agonist in Pulmonary arterial Hypertension) trial, which is enrolling patients around the world.

#### **About GRIPHON**

GRIPHON is a multicenter, double-blind, placebo-controlled morbidity/mortality Phase III trial evaluating the efficacy and safety of oral selexipag in patients with pulmonary arterial hypertension. The primary endpoint of the trial is to demonstrate the effect of Selexipag on the time to first clinical event of morbidity or mortality in patients with PAH. This trial is being conducted under an agreed special protocol assessment (SPA) with the U.S. Food and Drug Administration.

#### **About Actelion's PAH Franchise**

Actelion is dedicated to providing best-in-class therapies and industry leading resources for people living with PAH. Actelion's commercial product portfolio consists of market leading oral therapy Tracleer<sup>®</sup>, a dual endothelin receptor antagonist and in the US, inhaled prostacyclin Ventavis<sup>®</sup> as well as the recently launched Epoprostenol for Injection which provides added convenience for patients. In addition to its marketed products, Actelion leads the way in cutting edge science to advance PAH care with a pipeline of clinical candidates. Macitentan and selexipag are currently being evaluated in pivotal Phase III trials, and have the potential to become the next generation of care for patients. Further highlighting its commitment to patients, Actelion sponsors the REVEAL registry, the world's largest PAH patient registry, which provides a complete picture of the PAH treatment landscape and ultimately improves patient care.

#### **About Selexipag**

Selexipag (proposed INN, previously known as ACT-293987 or NS-304), originally discovered and synthesized by Nippon Shinyaku, is a first-in-class, orally available, selective IP receptor agonist which exerts vasodilating effects. [4,5] The selexipag ATS abstract can be found by clicking on following link:

<https://cms.psav.com/cAbstract/itinerary/day.html> [Search ACT-293987].

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## **Notes to Editor:**

### **About the American Thoracic Society (ATS) International Conference 2010**

The annual International Conference is being held in New Orleans and offers many sessions and several speakers on important scientific and clinical advances in pulmonary, critical care, and sleep medicine.

### **About Professor G. Simonneau MD, PhD**

Gérald Simonneau, MD, PhD is Chief of the Department of Pneumology, Hospital Antoine Bécère, Clamart, France. Professor Simonneau is past-President of the working Group on Pulmonary Circulation of the European Society of Cardiology. He has published widely in the fields of pulmonary hypertension, pulmonary vascular diseases, and pneumology. Professor Simonneau has been Director of the *Unité Propre de Recherche de l'Enseignement Supérieur* on pulmonary vascular diseases since 1998.

### **About the Phase II study with selexipag**

The study was a multicenter, double-blind, randomized, placebo-controlled study evaluating efficacy and safety of selexipag in PAH patients. The primary endpoint was pulmonary vascular resistance. The study was completed in July 2009 with 43 patients randomized 3:1.

### **About 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 function of the heart and lungs is severely compromised, manifested by a limited exercise capacity, and, ultimately, a reduced life expectancy. Approximately 100,000 people in Europe and the United States are afflicted with either primary or secondary forms of the disease related to conditions or tissue disorders that affect the lungs, such as scleroderma, lupus, HIV/AIDS or congenital heart disease.

PAH is associated with structural changes in both the pulmonary vasculature and the right ventricle. Recent advances [1] in the understanding of the pathogenic factors leading to the pulmonary vascular disease have led to the development of new therapies targeting specific pathways (the prostacyclin pathway; the endothelin pathway; and the nitric oxide pathway) [2]. The available therapies have positive effects in PAH, but they do not provide a cure, and in many patients the disease will progress. PAH remains a serious life-threatening condition [2,3]. Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

### **About prostacyclin**

Prostacyclin and prostaglandins are types of prostanoids. Endothelial cells produce several vasoactive chemical factors, among them prostacyclin (PGI<sub>2</sub>), which induce vasodilation of blood vessels and inhibit smooth muscle cell proliferation and platelet aggregation. The peptide endothelin is also produced by the endothelium, and is a potent constrictor of blood vessels and promotes cell proliferation. In a normal healthy state, prostacyclin helps counter-balance the actions of endothelin. In certain disease conditions, however, production of prostacyclin by the endothelium is impaired, allowing the deleterious effects of excessive levels of endothelin to predominate.

### **About prostacyclin receptor agonism**

The IP receptor (PGI<sub>2</sub> (prostacyclin) receptor) is one of 5 types of prostanoid receptor available to prostanoid replacement therapies. Prostacyclin activates the IP receptor inducing vasodilation and inhibiting proliferation of vascular smooth muscle cells. With selective IP receptor agonism, the risk of side effects mediated by activation of other prostanoid receptors is minimized.

Actelion is developing a first-in-class, orally available, selective IP receptor agonist that mimics the actions of endogenous prostacyclin for the treatment of PAH.

## References

1. Farber HW; Loscalzo J. Mechanisms of disease: pulmonary arterial hypertension. N. Eng. J. Med. 2004; 351: 1655-65.
2. Humbert M; Sitbon O; Simonneau G. Treatment of pulmonary arterial hypertension. N. Eng. J. Med. 2004;351:1425-36.
3. Humbert M; Morrell NW; Archer SL; et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J. Am. Coll. Cardiol. 2004; 43: Suppl. 12: 13S-24S.
4. Kuwano et al (2008). A long-acting and highly selective prostacyclin receptor agonist prodrug, 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), ameliorates rat pulmonary hypertension with unique relaxant responses of its active form, {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl) amino]butoxy}acetic acid (MRE-269), on rat pulmonary artery. J Pharmacol Exp Ther 326: 691-699
5. Kuwano et al (2007). 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug. J Pharmacol Exp Ther 322: 1181-1188.

## 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-in-class orally-available, selective IP receptor agonist for patients suffering from pulmonary arterial hypertension (PAH). This compound was originally discovered and synthesized by Nippon Shinyaku. Phase II evaluation has been completed, and a Phase III program in PAH patients has been initiated. 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.

## Nippon Shinyaku

For further information on Nippon Shinyaku please visit:

<http://www.nippon-shinyaku.co.jp/english/index.html>

## Actelion Ltd

Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion's first drug Tracleer<sup>®</sup>, an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer<sup>®</sup> 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<sup>®</sup>).

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