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New Post-hoc Analysis Shows Adding UPTRAVI® (selexipag) Versus Placebo Improved Long-Term Clinical Outcomes Regardless of Time of Treatment Initiation, and Demonstrated an Even More Pronounced Treatment Effect When Initiated Early

Actelion presents latest post-hoc analysis from the GRIPHON study – the largest randomized, controlled, outcome trial ever conducted in patients with pulmonary arterial hypertension (PAH)

ALLSCHWIL, SWITZERLAND – May 20, 2019 – Actelion Pharmaceuticals Ltd, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, has presented results of a *post-hoc* exploratory analysis of the GRIPHON study in patients with pulmonary arterial hypertension (PAH) showing that treatment with UPTRAVI® versus placebo improved clinical outcomes regardless of the time from diagnosis to UPTRAVI initiation, and that the treatment effect was more pronounced in those receiving UPTRAVI soon after diagnosis.¹ The data were presented at the annual American Thoracic Society International Conference in Dallas, Texas.

“This new analysis reinforces the overall efficacy data for selexipag and provides compelling evidence of the benefits of initiating selexipag early,” said Prof. Sean Gaine*, MD, Consultant Respiratory Physician and Director of National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin, Ireland. “These data add to the growing evidence supporting early intensification of treatment, which is important when you consider that around a third of PAH patients currently die within five years of diagnosis.^{2,3} Early recognition and prompt treatment of the disease are key to achieving sustained long-term benefits.”

The GRIPHON study evaluated the long-term efficacy and safety of oral UPTRAVI in 1,156 patients with PAH across 181 centers from 39 countries.⁴ It is the largest randomized, controlled, outcome trial ever conducted in patients with PAH, and demonstrated a 40% reduction in the primary composite endpoint of morbidity/mortality, defined as disease progression, worsening of PAH resulting in hospitalization, initiation of intravenous [IV] prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy, or death from any cause.⁴ Overall, the most common adverse events for patients receiving UPTRAVI were headache, diarrhea, nausea, and jaw pain.⁴

“The GRIPHON study firmly established the importance of the prostacyclin pathway in PAH treatment which will, hopefully, benefit patients worldwide,” said Richard Channick*, MD, Professor of Medicine and Director, Acute and Chronic Thromboembolic Disease Program at UCLA Medical Center. “This new analysis clearly demonstrates that early treatment is critical if we are to significantly improve long-term outcomes in this serious, progressive disease.”

This *post-hoc* analysis evaluated the impact of time from diagnosis to initiation of UPTRAVI on the treatment response with respect to the primary endpoint of the study. Patients were categorized at baseline based on their time from diagnosis using a six-month threshold. Patients treated earlier were defined as those who received treatment ≤6 months from diagnosis (N=404), and those who were treated later received treatment >6 months from diagnosis (N=752). UPTRAVI reduced the risk of

morbidity/mortality, compared with placebo, in both groups with a risk reduction of 55% for those treated earlier (HR 0.45 [95% CI: 0.33–0.63]) and a risk reduction of 30% for those treated later (HR 0.70 [95% CI: 0.54–0.91]). The response was more pronounced in those treated earlier. This pattern was observed in all background PAH therapy subgroups.

The results of the analysis are consistent with other studies and clinical guidelines that support the early initiation of treatment for PAH.

“This *post-hoc* analysis of the GRIPHON study adds to the growing body of research which indicates that selexipag can have a significant impact on a patients’ morbidity and disease progression, irrespective of background therapy,” said Alessandro Maresta, MD, VP and Head of Medical Affairs at Actelion Pharmaceuticals Ltd. “At Actelion, we have helped impact the lives of more than 300,000 patients with PAH globally over the past 20 years. Today it is essential that current treatments are used to their fullest potential so that we slow disease progression and significantly improve outcomes.”

UPTRAVI is an oral selective prostacyclin IP receptor agonist, and is available for the treatment of PAH in more than 40 countries. In the US, UPTRAVI is indicated for the treatment of PAH to delay disease progression and reduce the risk of hospitalization.⁵ In Europe, UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.⁶

**Drs. Gaine and Channick have received research support from Actelion and have served as paid consultants to the company.*

Notes to the Editor

ABOUT PULMONARY ARTERIAL HYPERTENSION (PAH)

PAH is a specific form of PH that causes the walls of the pulmonary arteries (blood vessels leading from the right side of the heart to the lungs) to become thick and stiff, narrowing the space for blood to flow, and causing an increased blood pressure to develop within the lungs. PAH is a serious, progressive disease with a variety of etiologies, and has a major impact on patients’ functioning, as well as their physical, psychological and social wellbeing. There is currently no cure for PH and it is often fatal.^{2,7,8} However, the last decade has seen significant advances in the understanding of the pathophysiology of PAH, transforming the prognosis for PAH patients from symptomatic improvements in exercise tolerance 10 years ago, to delayed disease progression today.

ABOUT THE POST-HOC ANALYSIS OF THE GRIPHON TRIAL

In the post-hoc analysis of the GRIPHON trial, UPTRAVI reduced the risk of morbidity/mortality compared with placebo in both subgroups, with a more pronounced treatment effect in those treated earlier (HR [95% CI] 0.45 [0.33-0.63]) than in those treated later (0.70 [0.54-0.91]). Results were consistent when adjusting for baseline covariates PAH therapy (categorized as yes/no), WHO FC, sex, race, age (categorized as < 65/≥ 65 years), etiology, geographical region, 6MWD and NT pro-BNP: HR (95% CI) 0.47 (0.33-0.65) in those treated earlier and 0.74 (0.57-0.96) in those treated later.¹

ABOUT UPTRAVI® (selexipag)

UPTRAVI, originally discovered and synthesized by Nippon Shinyaku, is an oral selective prostacyclin IP receptor agonist for the treatment of PAH. UPTRAVI is the only globally-available oral treatment that works on the prostacyclin pathway with evidence of long-term outcomes. UPTRAVI is available for the treatment of PAH in more than 40 countries. In the US, UPTRAVI is indicated for the treatment of PAH to delay disease progression and reduce the risk of hospitalization.⁵ In Europe, UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.⁶

The efficacy of UPTRAVI in PAH was established in GRIPHON (Prostacyclin (PGI₂) Receptor agonist In Pulmonary arterial HypertensiON), the largest randomized, controlled trial ever conducted in PAH patients. This double-blind, multicenter study aimed to evaluate the long-term efficacy and safety of

oral UPTRAVI and included almost 400 patients who were already receiving double combination PAH treatment. The study provided the first randomized, controlled evidence for triple oral combination therapy in PAH. UPTRAVI was shown to delay disease progression and significantly reduce the risk of hospitalization compared with placebo, as well as improving exercise capacity.⁴ Overall, the most common adverse events in the UPTRAVI group were consistent with the known side effects of prostacyclin, including headache, diarrhea, nausea, and jaw pain.⁴

What is the most important information about UPTRAVI?

What is UPTRAVI?

UPTRAVI® (selexipag) is a prescription medicine used to treat pulmonary arterial hypertension (PAH, WHO Group 1), which is high blood pressure in the arteries of your lungs.

UPTRAVI can help slow down the progression of your disease and lower your risk of being hospitalized for PAH.

It is not known if UPTRAVI is safe and effective in children

Who should not take UPTRAVI?

- Do not take UPTRAVI if you take gemfibrozil because this medicine may affect how UPTRAVI works and cause side effects

What should I tell my doctor before taking UPTRAVI?

Tell your doctor if you:

- Have liver problems
- Have narrowing of the pulmonary veins (veins in your lungs). This is called pulmonary veno-occlusive disease (PVOD)
- Are pregnant or plan to become pregnant. It is not known if UPTRAVI will harm your unborn baby
- Are breastfeeding or plan to breastfeed. It is not known if UPTRAVI passes into your breast milk. You and your doctor should decide if you will take UPTRAVI or breastfeed. You should not do both
- Have any other medical conditions
- Are taking any other prescription or over-the-counter medicines, vitamins, or herbal supplements

What are the possible side effects of UPTRAVI?

The most common side effects are:

- Headache
- Nausea
- Pain in arms or legs
- Low red blood cell count
- Diarrhea
- Muscle pain
- Temporary reddening of the skin (flushing)
- Less appetite than usual
- Jaw pain
- Vomiting
- Joint pain
- Rash

Talk to your doctor if you have a side effect that bothers you or does not go away. These are not all the possible side effects of UPTRAVI. For more information, ask your doctor or pharmacist.

You may report side effects to **FDA at 1-800-FDA-1088** or www.fda.gov/medwatch.

Keep UPTRAVI and all medicines out of the reach of children.

What other medicines might interact with UPTRAVI?

- UPTRAVI and other medicines may affect each other, causing side effects. Tell your doctor about all the medicines you are taking. Do not start any new medicine until you check with your doctor

How should I take UPTRAVI?

- Take UPTRAVI exactly as your doctor tells you to take it. Usually, your doctor will have you take UPTRAVI twice a day. Taking UPTRAVI with food may help you tolerate UPTRAVI better
- Swallow UPTRAVI tablets whole. Do not split, crush, or chew tablets
- Tell your doctor if you have any form of liver disease. Your doctor may need to change your dose of UPTRAVI
- UPTRAVI is measured in micrograms (mcg). Tablets come in the following strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

Please see full [Prescribing Information](#) and [Patient Product Information](#).

ABOUT ACTELION

In June 2017, Actelion became part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Actelion's medicines have helped to expand and strengthen Janssen's portfolio with leading, differentiated in-market medicines and promising late-stage compounds. Janssen has added Pulmonary Hypertension as a therapeutic area of focus to maintain the leadership position Actelion has built in this important disease area. Learn more at www.actelion.com. Follow us on Twitter @actelion_com.

ABOUT THE JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology and Pulmonary Hypertension. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal. Actelion Pharmaceuticals Ltd is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding UPTRAVI® (selexipag). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Actelion Pharmaceuticals Ltd, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors", and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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