

Interim Analysis Showed Treatment with OPSUMIT® (macitentan) Associated with Significant Improvement in Right Ventricular (RV) Function and Pulmonary Vascular Resistance (PVR) in Patients with Pulmonary Arterial Hypertension (PAH)

Actelion Presents REPAIR Study Interim Analysis at the American College of Cardiology's 68th Annual Scientific Session



SOUTH SAN FRANCISCO, Calif. and ALLSCHWIL, Switzerland, March 15, 2019 /PRNewswire/ - Actelion Pharmaceuticals US, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, announced today an interim analysis from the **Right vEntricular Remodeling in Pulmonary Arterial hypertension (REPAIR)** study of OPSUMIT® (macitentan) that shows treatment with OPSUMIT in patients with pulmonary arterial hypertension (PAH) was associated with significant improvements in right ventricular (RV) function including reversal of RV remodeling and reduced pulmonary vascular resistance (PVR). The data are being presented at the American College of Cardiology's 68th Annual Scientific Session.

"The REPAIR study is the first multicenter study in PAH to use a primary endpoint measured by cardiac MRI," said Stephan Rosenkranz, MD, Head of Pulmonary Hypertension Center and Head of Cologne Cardiovascular Research Center (CCRC), University of Cologne, Division of Cardiology. "These results offer clinicians who treat this severe and progressive disease a better understanding of the effects that macitentan can have on RV remodeling and function in patients with PAH."

The REPAIR study is a 52-week, open-label, multicenter study evaluating the effect of OPSUMIT on RV remodeling and function as determined by cardiac magnetic resonance imaging (MRI) and right heart catheterization. OPSUMIT was initiated as monotherapy or sequential combination therapy with a phosphodiesterase-type 5 (PDE-5) inhibitor or as initial combination therapy with a PDE-5 inhibitor. The pre-specified interim analysis including 42 patients with PAH showed significant improvements in both primary endpoints including a 15.2 mL mean increase ($p < 0.0001$) in RV stroke volume (RVSV) and a 37% reduction ($p < 0.0001$) in PVR from baseline at Week 26. RVSV was determined by pulmonary artery flow MRI and PVR was measured by right heart catheterization. A full evaluation, with focus on RV, was also performed using MRI.

"Measurement of RV function in patients with PAH is very helpful in monitoring response to treatment," said Richard N. Channick, MD, Professor of Medicine and Director, Acute and Chronic Thromboembolic Disease Program at UCLA Medical Center. "The REPAIR study shows us that RV function, as determined by MRI, is a relevant endpoint in studying treatment efficacy in PAH."

Pulmonary arterial hypertension is a progressive disease in which blood vessels in the lungs become restricted. This forces the right heart to work harder to pump blood to the lungs, and RV function is impaired. The results from the REPAIR interim analysis suggest that treatment with OPSUMIT is associated with significantly improved RV function as determined by MRI in patients with PAH. In the REPAIR study, the safety profile of OPSUMIT was consistent with previous clinical trial data. These results add to the growing body of research into understanding OPSUMIT in PAH.

"We are very pleased with these interim results from the REPAIR study and we will work diligently to report the full study results in the near future," said Alessandro Maresta, MD, VP and Head of Global Medical Affairs at Actelion Pharmaceuticals Ltd. "We are committed to ongoing research and to advancing therapies for people with PAH and are proud to make a difference in patients' lives."

**Drs. Rosenkranz 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)

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.

ABOUT THE REPAIR STUDY

The **Right vEntricular Remodeling in Pulmonary ArterIal hypeRtension (REPAIR)** study is a 52-week, open-label, multicenter study evaluating the effect of OPSUMIT on right ventricular (RV) remodeling and function as determined by cardiac MRI and right heart catheterization. REPAIR is the first multicenter study in PAH to use a primary endpoint measured by MRI enabling clinicians to further understand the direct effects of OPSUMIT on RV remodeling and function in patients with PAH.

In the REPAIR study, OPSUMIT was initiated as monotherapy or sequential combination therapy with a phosphodiesterase-type 5 (PDE-5) inhibitor or as initial combination therapy with a PDE-5 inhibitor. The two primary endpoints were (1) change in RVSV from baseline to Week 26, determined by pulmonary artery flow MRI, and (2) change in PVR from baseline to Week 26 measured by right heart catheterization. In the pre-specified interim analysis including the first 42 patients enrolled, RVSV was significantly increased (mean change 15.2 ml, 96% CI [9.3; 21.0], $p < 0.0001$) and PVR was significantly decreased (37%, 99% CI [26; 46], $p < 0.0001$) at Week 26. The study was declared positive and enrollment was stopped. All enrolled patients remain in the study up to their 52-week assessments, and a supportive final analysis will be presented when the results become available.

The REPAIR study showed that treatment with OPSUMIT was associated with significant improvement in RV function in patients with PAH.

What is OPSUMIT® (macitentan)?

OPSUMIT is a prescription medicine used to treat pulmonary arterial hypertension (PAH, WHO Group 1). PAH is high blood pressure in the arteries of your lungs. OPSUMIT can:

- Improve your ability to exercise as measured by the 6-minute walk distance (6MWD). In a clinical study of mainly WHO FC II-III patients, those taking OPSUMIT walked, on average, 22 meters farther at Month 6 than patients not taking it
- Improve some of your symptoms
- Help slow down the progression of your disease
- Lower your chance of being hospitalized for PAH

It is not known if OPSUMIT is safe and effective in children.

The most important information about OPSUMIT® (macitentan)

Do not take OPSUMIT if you are pregnant or trying to get pregnant. OPSUMIT can cause serious birth defects if taken while pregnant.

Women who are able to get pregnant must have negative pregnancy tests:

- Before starting OPSUMIT
- Each month while taking OPSUMIT
- For 1 month after stopping OPSUMIT

Your doctor will decide when you should take pregnancy tests.

You are medically able to get pregnant if you are a woman who fits all of the following guidelines:

- has started puberty, even if you have not had a menstrual period yet
- has a uterus
- has not gone through menopause (menopause means you have not had a menstrual period for at least 12 months for natural reasons, or have had your ovaries removed)

You are not medically able to get pregnant if you are a woman who fits at least 1 of the following guidelines:

- has not started puberty
- does not have a uterus
- has gone through menopause (you have not had a menstrual period for at least 12 months for natural reasons, or have had your ovaries removed)
- is infertile for other medical reasons and this infertility is permanent and cannot be reversed

While taking OPSUMIT, and for 1 month after stopping OPSUMIT, women who are able to get pregnant must use 2 acceptable forms of birth control. Women who have had a tubal sterilization, a progesterone implant, or have an IUD (intrauterine device) do not need a second form of birth control. Talk to your doctor or gynecologist about which birth control to use while on OPSUMIT. If you decide to change your form of birth control, talk with your doctor or gynecologist. This way you can be sure to choose another acceptable form of birth control. **Also review the Medication Guide for acceptable birth control options.**

It's important not to have unprotected sex while taking OPSUMIT. Tell your doctor right away if you have unprotected sex, think your birth control has failed, miss a menstrual period, or think you may be pregnant. He or she may recommend using a form of emergency birth control.

If you are the parent or caregiver of a female child who started taking OPSUMIT before reaching puberty, check with your child regularly for any signs of puberty. **Your child may reach puberty before having**

her first menstrual period. Talk to your doctor if you think your child is showing signs of puberty or if you have any questions about the signs of puberty.

Before starting OPSUMIT, women must enroll in a program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS). If you are a woman who is able to get pregnant, you must talk to your doctor to learn the benefits and risks of OPSUMIT. You must also agree to all of the instructions in the program. Men who are prescribed OPSUMIT do not need to enroll in this program.

Who should not take OPSUMIT?

Do not take OPSUMIT if you are pregnant, plan to become pregnant, or become pregnant during treatment with OPSUMIT. OPSUMIT can cause serious birth defects. See "[The most important information about OPSUMIT.](#)"

Talk to your doctor about all your medical conditions, as well as all the medicines, vitamins, and supplements you take. OPSUMIT and other medicines may affect each other causing side effects. Tell your doctor right away if you take an HIV medicine. Do not start any new medicine until you check with your doctor.

What should I avoid while taking OPSUMIT?

- **Do not get pregnant.** OPSUMIT can cause serious birth defects. See "[The most important information about OPSUMIT.](#)" If you miss a menstrual period or think you may be pregnant, call your doctor right away
- **You should not breastfeed if you take OPSUMIT.** It is not known if OPSUMIT passes into your breast milk. Talk to your doctor about the best way to feed your baby

What are the possible side effects of OPSUMIT?

OPSUMIT can cause serious side effects, including:

- **Serious birth defects.** See "[The most important information about OPSUMIT](#)"
- **Some medicines that are like OPSUMIT can cause liver problems.** Your doctor should do blood tests to check your liver before you start OPSUMIT. Tell your doctor if you have any of these symptoms, which could be a sign of liver problems while on OPSUMIT:
 - Nausea or vomiting
 - Pain in the upper right stomach
 - Feeling tired
 - Loss of appetite
 - Your skin or the whites of your eyes turn yellow
 - Dark urine
 - Fever
 - Itching
- **Fluid retention** could happen during the first weeks after starting OPSUMIT. Tell your doctor right away if you notice unusual weight gain or swelling in your ankles or legs. Your doctor will look for the cause
- **Low red blood cell levels (anemia) can happen while taking OPSUMIT, usually during the first weeks after starting OPSUMIT. In some cases a blood transfusion may be needed, but this is not common.** Your doctor will do blood tests to check for anemia before you start OPSUMIT. You may also need to do these blood tests while taking OPSUMIT
- **Decreased sperm counts.** OPSUMIT, and other medicines like OPSUMIT, may cause decreased sperm counts in men who take these medicines. If fathering a child is important to you, tell your doctor

The most common side effects are:

- Stuffy nose or sore throat
- Irritation of the airways (bronchitis)
- Headache
- Flu
- Urinary tract infection

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 OPSUMIT. 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.

Please see full Prescribing Information and Medication Guide, including an Important Warning about Serious Birth Defects at <http://opsumit.com/opsumit-prescribing-information.pdf>.

ABOUT ACTELION

Actelion, a leader in Pulmonary Arterial Hypertension, became part of the Janssen Pharmaceutical Companies of Johnson & Johnson following its acquisition in June 2017. 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 within this rare disease area. Learn more at www.actelion.com. Follow us at [@actelion_com](https://twitter.com/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](https://twitter.com/JanssenGlobal) and [www.twitter.com/JanssenUS](https://twitter.com/JanssenUS). Actelion Pharmaceuticals US, Inc. 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 the development of OPSUMIT® (macitentan). 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 US, Inc., 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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