News Release

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Late-Breaking Phase 3 A DUE Data Show Investigational Single Tablet Combination Therapy of Macitentan and Tadalafil Significantly Improves Pulmonary Hemodynamics versus Monotherapy in Patients with Pulmonary Arterial Hypertension (PAH)

Study findings presented during the American College of Cardiology's 72nd Annual Scientific Session & Expo Together With World Heart Federation's World Congress of Cardiology

European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines recommend initial dual combination therapy with macitentan and tadalafil for PAH patients without cardiopulmonary comorbidities

RARITAN, NJ, March 6, 2023 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results from the Phase 3 A DUE study (NCT03904693), which showed an investigational once-daily, single tablet combination therapy, also known as fixed dose combination, of macitentan 10 mg and tadalafil 40 mg (M/T STCT), significantly improved pulmonary hemodynamics (blood flow through pulmonary blood vessels) versus macitentan and tadalafil monotherapies in pulmonary arterial hypertension (PAH) patients with World Health

Organization (WHO) functional class (FC) II or III.[1] The data were presented today as a Late-Breaking Clinical Trial presentation during the American College of Cardiology's 72nd Annual Scientific Session & Expo Together With World Heart Federation's World Congress of Cardiology.

PAH is a rare, progressive and life-threatening blood vessel disorder characterized by the constriction of small pulmonary arteries and elevated blood pressure in the pulmonary circulation that eventually leads to right heart failure.[2] Recently updated European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines[i] have recommended initial dual combination therapy with macitentan and tadalafil for PAH patients without cardiopulmonary comorbidities. Currently, this requires patients to take multiple pills as no single tablet that combines two or more PAH-specific pathways is available for these patients.[3]

"Targeting different pathways in the treatment of PAH has demonstrated clear clinical benefits, yet current treatment regimens are cumbersome and create a significant pill burden for patients, many of whom take a large number of pills each day to treat their PAH and various co-morbidities,[ii,iii]" said Kelly Chin, M.D., Professor of Internal Medicine and Director of the Pulmonary Hypertension Program at UT Southwestern Medical Center, and an investigator in the A DUE study.[4] "The results from this study demonstrate that a single tablet combination has the potential to support initial dual combination therapy and rapid escalation from monotherapy, which may improve functional outcomes and help close the gap from guideline recommendations to clinical practice."

The A DUE study is a double-blind, randomized, active-controlled, multi-center, adaptive parallel-group study designed to compare the efficacy and safety of

[1] WHO FC II/III is defined as slight or marked limitation of physical activity with ordinary or less than ordinary activity causing undue shortness of breath or fatigue, chest pain, or near fainting.
[2] Right heart failure occurs when the heart's right ventricle is too weak to pump enough blood to the lungs.
[3] OPSYNVI® (macitentan 10 mg and tadalafil 40 mg) was approved in Canada in October 2021 and in Argentina in October 2022 but only for substitution indication (for PAH patients who are already treated with combination of macitentan 10 mg and tadalafil 40 mg as separate tablets).
[4] Dr. Chin was compensated for her participation on the steering committee for the A DUE study.

investigational M/T STCT versus macitentan and tadalafil monotherapies in patients with PAH. A total of 187 adult PAH patients from across 148 sites in 19 countries worldwide in WHO FC II or III who were treatment naïve or on a stable dose of an endothelin receptor antagonist (ERA) or a phosphodiesterase type 5 inhibitor (PDE5i) for at least three months, were enrolled in the study. The primary endpoint is pulmonary vascular resistance (PVR) measured 16 weeks following initiation of treatment expressed as the ratio of geometric means to baseline.

Secondary efficacy outcome measures included change from baseline in exercise capacity as measured by change in 6-minute walk distance (6MWD) at the end of double-blind treatment at week 16 compared to baseline.

Following the double-blind treatment period, patients transitioned to the open-label treatment period for 24 months. Baseline characteristics were balanced across treatment arms except for a higher proportion of WHO FC II patients in the M/T STCT arm and a greater time from diagnosis of PAH in the macitentan arm.

"The guiding light of our PH research is the goal of transforming PAH into a manageable condition, so we're constantly looking for ways to improve both clinical outcomes and the treatment experience," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular, Metabolism, Retina & Pulmonary Hypertension, Janssen Research & Development, LLC. "A single tablet combination has the potential to be an important new option for helping physicians optimize disease management with the potential to enhance convenience and help improve adherence and outcomes."

Key A DUE Study Findings

The A DUE study met its co-primary endpoint, demonstrating marked pulmonary hemodynamic improvement as shown by the highly statistically significant, consistent and robust PVR reduction in participants treated with M/T STCT compared to both monotherapies. PVR change with M/T STCT was significantly greater versus macitentan (treatment effect: 29%; 95% confidence limit [CL]: -

18%, -39%, p<0.0001). PVR change with M/T STCT was also significantly greater versus tadalafil (treatment effect: 28%; 95% CL: -20%, -36%, p<0.0001).

Although the A DUE study was not powered to demonstrate a benefit on exercise capacity, there was a clinically relevant improvement in 6MWD.

- At week 16, treatment effect was not statistically significant; however, a clinically relevant improvement in 6MWD in favor of M/T STCT versus monotherapies was observed. Adjusted treatment effect in 6MWD, change from baseline, in the M/T STCT versus macitentan group was 16.04m (CL: -17.0, 49.08, p=0.380) and 25.37m in the M/T STCT versus tadalafil group (CL: -0.93, 51.59, p =0.059).
- The safety profile of M/T STCT was consistent with the known safety profiles of macitentan and tadalafil monotherapies and no new safety observations were made.

About macitentan/tadalafil STCT

Macitentan 10 mg and tadalafil 40 mg STCT is an investigational therapy that combines the ERA, macitentan, and the PDE5i, tadalafil.

About OPSUMIT® (macitentan)

OPSUMIT® is indicated for the treatment of PAH (WHO Group I) to reduce the risks of disease progression and hospitalization for PAH. The use of OPSUMIT® in patients with PAH (WHO Group I), a type of PH, was demonstrated in the pivotal SERAPHIN trial, the largest (n=742) long-term (average treatment duration=2 years) outcomes-based trial of an ERA in PAH.

About tadalafil

Tadalafil is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

OPSUMIT® INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

OPSUMIT® (macitentan) is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. 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%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT® to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSUMIT® is available only through a restricted program called the OPSUMIT® Risk Evaluation and Mitigation Strategy (REMS).**

CONTRAINDICATIONS

Pregnancy: OPSUMIT® may cause fetal harm when administered to a pregnant woman. OPSUMIT® is contraindicated in females who are pregnant. If OPSUMIT® is used during pregnancy, advise the patient of the potential risk to a fetus.

Hypersensitivity: OPSUMIT® is contraindicated in patients with a history of a hypersensitivity reaction to macitentan or any component of the product.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT® REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT® is available for females only through a restricted program called the OPSUMIT® REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT® REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT® REMS Program prior to initiating OPSUMIT®. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT®.

Hepatotoxicity

- ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 x ULN was 3.4% for OPSUMIT® vs 4.5% for placebo, and >8 x ULN was 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT® vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT® and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).

- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT®. Consider re-initiation of OPSUMIT® when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Fluid Retention

- Peripheral edema and fluid retention are known consequences of PAH and ERAs. In the pivotal PAH study SERAPHIN, edema was reported in 21.9% of the OPSUMIT® group vs 20.5% for placebo.
- Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of pulmonary hypertension due to left ventricular dysfunction, more patients in the OPSUMIT® group developed significant fluid retention and had more hospitalizations due to worsening heart failure compared to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT®, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported.
- Monitor for signs of fluid retention after OPSUMIT® initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the possible need to discontinue OPSUMIT®.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT®. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT® caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT® group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.

- Initiation of OPSUMIT® is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT®.

Decreased Sperm Counts

OPSUMIT®, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT® with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT® with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.
- Moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole and amiodarone are predicted to increase macitentan exposure. Avoid concomitant use of OPSUMIT® with moderate dual inhibitors of CYP3A4 and CYP2C9.

- Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSUMIT® should also be avoided.

Please see full Prescribing Information, including BOXED WARNING.

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 & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at @JanssenGlobal and @JanssenUS. Janssen Research & Development, LLC is part 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 product development and the potential benefits and treatment impact of macitentan/tadalafil STCT. 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 Janssen Research & Development, LLC 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; competition, including technological advances, new products and patents attained by competitors; challenges to patents; 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 January 1, 2023, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in

Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other 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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[i] 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2022) 43, 3618–3731. https://doi.org/10.1093/eurheartj/ehac237.
[ii] Grady D, et al. *Pulm Circ* 2018; 8:1–9; 6.
[iii] Lauffenburger JC, et al*. J Gen Intern Med* 2017.

