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Evaluating Right Ventricular Stroke Volume and Pulmonary Vascular Resistance in PAH

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled, “The REPAIR Study: Evaluating Right Ventricular Stroke Volume and Pulmonary Vascular Resistance in PAH,” is an educational activity brought to you by the Janssen Pharmaceutical Companies of Johnson & Johnson, the marketer and distributor of OPSUMIT® (macitentan). Please see full Prescribing Information for OPSUMIT® at www.opsumithcp.com. This program is intended for US healthcare professionals only and is not certified for continuing medical education.

Our guest today is pulmonologist and critical care medicine specialist Dr. Richard Channick, who is a paid consultant for the Janssen Pharmaceutical Companies of Johnson & Johnson. Dr. Channick is presenting on behalf of Janssen and must present information in compliance with FDA requirements applicable to Janssen.

And now here is your host, Dr. Randy Young, a paid consultant for ReachMD.

ReachMD Host, Dr. Young:
This is ReachMD, and I'm Dr. Randy Young. Today, we'll be speaking with Dr. Channick about the REPAIR study, an open-label, single-arm Phase 4 study that aimed to evaluate the effect that OPSUMIT® had on RV stroke volume, or RVSV, and pulmonary vascular resistance, or PVR, in people with pulmonary arterial hypertension, or PAH.[1]

Dr. Channick, thanks for being here today.

Announcer:
First, let’s review the indication for OPSUMIT®.

OPSUMIT® is an endothelin receptor antagonist 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 and III symptoms treated for an average of 2 years. 57% of patients had idiopathic and heritable PAH, 31% of patients had PAH caused by connective tissue disorders, and 8% of patients had PAH caused by congenital heart disease with repaired shunts.

Now we will review the Boxed Warning for OPSUMIT®.

OPSUMIT® has a Boxed Warning for 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).

Dr. Young:
To get started, Dr. Channick, can you explain a little bit about pulmonary arterial hypertension and its effect on the heart?

Dr. Channick:
Sure, Dr. Young. Thank you for having me here today.

PAH is a rare disease with approximately 500 to 1,000 new cases diagnosed in the U.S. each year, and it has a traditionally poor prognosis.[2,3] PAH is a progressive disease in which blood vessels in the lungs become constricted and narrowed, leading to elevation in the blood pressure in the pulmonary arteries. This high blood pressure forces the right ventricle of the heart to work harder to pump blood to the lungs. Over time, this can cause the right ventricle to become strained and not function properly.[4]

Given the progressive nature of PAH, clinical guidelines indicate that combination therapy may be appropriate for certain subsets of patients, whether given initially or sequentially.[4,5] A multi-parametric risk stratification approach can be used to determine if the escalation of therapy is warranted with the goal of getting the patient to low-risk status.[6,7]

Dr. Young:
Thank you for that background, Dr. Channick. Before we delve into the details of the REPAIR study, can you first walk us through the pivotal SERAPHIN study for OPSUMIT®?

Dr. Channick:
Absolutely, Dr. Young. In 2013, the FDA approved OPSUMIT ® based on the efficacy and safety established in a clinical trial called the "Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcomes," or SERAPHIN for short.8,9 SERAPHIN was the largest long-term outcomes-based pivotal trial of an endothelin receptor antagonist, or ERA, in PAH.[8,10] It included 742 patients with an average treatment duration of approximately 2 years.[8]

At study baseline, 36% of patients were not using PAH-specific background therapy, and 64% were using stable background therapy for at least 3 months with phosphodiesterase type 5 inhibitors, also called PDE-5 inhibitors, or inhaled or oral prostanoids for at least 3 months before randomization. It should be noted that OPSUMIT® is approved in combination with PDE-5 inhibitors or inhaled prostanoids, but not with oral prostanoids.[8]

In terms of patient demographics in the SERAPHIN study, patients had symptoms aligning predominantly with World Health Organization Functional Class (also known as WHO functional class) II and III; 52% and 46%, respectively. The etiology or cause of PAH included idiopathic or heritable PAH in 57% of study subjects, PAH associated with connective tissue disorders in 31% of subjects, PAH associated with congenital heart disease with repaired shunts in 8% of subjects, PAH associated with drugs or toxins in 3% of subjects, and PAH associated with HIV in the remaining 1% of study subjects.[8]

The average age of patients in the SERAPHIN trial was 46 years, and 77% of patients were female. Twenty-five percent of patients had been diagnosed with PAH recently, defined as less than 6 months prior to enrolling in the study, while 75% had been diagnosed with PAH for at least 6 months or longer before study enrollment.[8]

The primary endpoint in the SERAPHIN trial was time to the first occurrence of death or a significant morbidity event. For this trial, a significant morbidity event was defined as atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH. Clinical worsening of PAH was defined as a sustained decrease in six-minute walking distance of at least 15% from baseline, confirmed by a second 6-minute walk test performed on a different day within 2 weeks, worsened PAH symptoms, as defined by a decline in World Health Organization functional class, and need for additional PAH treatment.[8,9]

Results of SERAPHIN found that compared to placebo, OPSUMIT® 10 milligrams significantly reduced the risk of the first occurrence of a morbidity/mortality event by 45% based on a hazard ratio of 0.55 and a 97.5% confidence interval of 0.39 to 0.76.[9] This data was statistically significant, with a p-value of less than 0.0001. The beneficial effect of OPSUMIT® 10 milligrams was primarily attributable to reduction in clinical worsening events, as we defined previously. OPSUMIT® showed no difference in death as a single component of the composite primary endpoint.[8]

During the SERAPHIN trial, adverse reactions that were observed more frequently in patients on OPSUMIT® compared to placebo by greater than or equal to 3% were anemia at 13% versus 3%, nasopharyngitis or pharyngitis in 20% versus 13%, bronchitis in 12% versus 6%, headache in 14% versus 9%, influenza in 6% versus 2%, and urinary tract infection in 9% versus 6%. The overall incidence of treatment discontinuations due to adverse events with OPSUMIT® was similar to placebo, approximately 11%.[8]

Additional adverse events of special interest in the SERAPHIN trial were hypotension in 7% of patients on OPSUMIT® versus 4.4% on placebo, edema in 21.9% on OPSUMIT® versus 20.5% on placebo, and peripheral edema in 18.2% on OPSUMIT® versus 18.1% on

placebo. Further, instances of elevated liver enzymes at least 3 times above the upper limit of the normal range, or ULN, were observed in 3.4% of patients on OPSUMIT®, compared to 4.5% on placebo. While elevated liver enzymes at least 8 times above upper limits of normal were observed in 2.1% of patients on OPSUMIT®, compared to 0.4% on placebo. Decreased hemoglobin was observed in 8.7% of patients on OPSUMIT® compared to 3.4% on placebo.[8,9]

Dr. Young:
Thanks, Dr. Channick. And now, let's go over some additional Important Safety Information about OPSUMIT®.

Announcer:
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®.

Dr. Young:
Dr. Channick, we're ready to dive into the REPAIR study. Could you provide an overview of study subject demographics, objectives, and primary and secondary endpoints?

Dr. Channick:
Absolutely. REPAIR was a 52-week, prospective, multicenter, single-arm, open-label, Phase 4 study. The objectives of the REPAIR study were to evaluate the effect of OPSUMIT® on right ventricular and hemodynamic properties in patients with PAH, and to evaluate the safety and tolerability of OPSUMIT® in patients with symptomatic PAH.[1]

I'd like to take a moment to explain the different study populations. First, 42 patients were included in the primary interim analysis set. These patients received at least one dose of OPSUMIT® and had valid measurements for both primary endpoints at baseline and Week 26. The final analysis set included 71 patients, all of whom had both right ventricular stroke volume and pulmonary vascular resistance measures at baseline and Week 26. The safety set included 87 patients, all of whom received at least one dose of OPSUMIT®.[1]

Patients across the study also met the following inclusion criteria. All patients were between 18 and 74 years old, with a previous confirmed diagnosis of idiopathic or heritable PAH, PAH related to connective tissue disease, drug use or toxin exposure, or simple congenital systemic-to-pulmonary shunts at least 2 years after repair. All patients were PAH-treatment naïve or had been receiving a stable background PDE-5 inhibitor for at least 3 months, with a six-minute walking distance of at least 150 meters and a functional class between I and III. Finally, patients were excluded from the study if they had a history of ERAs, stimulators of soluble guanylate cyclase, or prostacyclin or prostacyclin analogues.[1]

There were two primary endpoints, right ventricular stroke volume, also called RVSV, determined by cardiac magnetic resonance, or CMR, and pulmonary vascular resistance, also called PVR, determined by right heart catheterization. Both were measured by change from baseline to Week 26 in the interim analysis and final analysis.[1]

The REPAIR study had several exploratory secondary endpoints related to right ventricular parameters, including end-systolic and end-diastolic volume, ejection fraction, mass assessed by cardiac magnetic resonance, 6-minute walk distance, and WHO functional class. All of the exploratory secondary endpoints were measured by change from baseline to Week 26 in the final analysis set of 71 patients. Now I do want to point out that the single-arm open-label design and study size of the REPAIR study limited subgroup analyses.[1]

In terms of patient demographics in the final analysis set of the REPAIR study, consisting of 71 patients, patients had predominantly WHO functional class II and III symptoms with 47.9% and 50.7% at baseline, respectively. The etiology or cause of PAH included idiopathic PAH in 59.2% of study subjects, PAH associated with connective tissue disorders, known as PAH-CTD in 28.2% of subjects, PAH associated with congenital heart disease known as PAH-CHD in 7% of subjects, heritable PAH in 2.8% of study subjects, and PAH associated with drug and toxin use in 2.8% of subjects.[1]

The median age of patients in the REPAIR trial was 45 years, and 80.3% were female. In 62% of patients, including those who were treatment naive, or those who had previously been taking background therapy with a PDE-5 inhibitor, OPSUMIT® was initiated alone, while 38% of patients were started on initial combination therapy, with both OPSUMIT® and a PDE-5 inhibitor.[1]

Dr. Young:
Thank you. Is there anything else we should know about REPAIR?

Dr. Channick:
Yes, there are some important considerations. First, the data are based on a single-arm, open-label clinical trial and not on a randomized, placebo-controlled clinical trial. In addition, cardiac magnetic resonance parameters have not been accepted as primary endpoints for pivotal studies in PAH, so these data are hypothesis generating, and further research is needed for a better understanding of the significance of CMR parameters as proxy for disease progression. Also, the open-label design and study size of the REPAIR study limited subgroup analysis.[1]

As we've established, OPSUMIT® is an ERA indicated for the treatment of PAH, WHO Group I, functional class II to III, to reduce the risk of disease progression and hospitalization for PAH.9 This uncontrolled study cannot be used to determine the effect of OPSUMIT®. The study was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson.[1]

Dr. Young:
For those just tuning in, you're listening to ReachMD. I'm Dr. Randy Young, and today I'm speaking with Dr. Richard Channick about the REPAIR study and a treatment option for pulmonary arterial hypertension.

Can you tell us about the study's results for the primary endpoints, Dr. Channick?

Dr. Channick:
Absolutely. It's important to note that REPAIR is the first prospective multicenter study in PAH to use right ventricular stroke volume as assessed by CMR as a primary endpoint. The second primary endpoint of the study was pulmonary vascular resistance, or PVR, as measured by right heart catheterization.[11] And what the study found was that at a pre-specified interim analysis of 42 patients, a statistically significant change from baseline was observed for both primary endpoints, and the study was declared positive, so enrollment was stopped.[1]

First, I'll go over the results for the primary endpoints from the interim analysis of 42 study participants. The study found there was a 15.2-milliliter increase in right ventricular stroke volume at Week 26 with a mean baseline of 50.7 milliliters, and there was a 37% decrease in pulmonary vascular resistance with a 0.63 dynes·sec/cm5 ratio of Week 26 over baseline from a mean baseline of 900.2 dynes·sec/cm5. In the final analysis set of 71 patients, which was consistent with the primary interim analysis set, the study found there was a 12.0-milliliter increase in right ventricular stroke volume at Week 26 from a mean baseline of 52.2 milliliters, and there was a 38% decrease in pulmonary vascular resistance with a 0.62 dynes·sec/cm5 ratio of Week 26 over baseline from the mean baseline of 974.6 dynes·sec/cm5.[1]

Observing changes in right ventricular stroke volume and pulmonary vascular resistance in participants in the REPAIR study, really helps us understand more about the potential impact of OPSUMIT®, either by itself or in combination with a PDE-5 inhibitor in patients with this rare disease.

Dr. Young:
What about the findings for the secondary endpoints of the REPAIR study? Can you help us understand those?

Dr. Channick:

Yes. Before we review the results, I'd like to note that these analyses are of an exploratory nature, as they were performed with no correction for multiple testing. In the final analysis set of 71 patients, the secondary endpoints were all assessed as change from baseline to Week 26.[1]

Let's start with the changes observed in right ventricular end-systolic volume, ejection fraction, and mass at Week 26. The study found a 16.1-milliliter decrease in right ventricular end-systolic volume from a mean baseline of 90.2 milliliters. And there was a 10.6% increase in right ventricle ejection fraction from pulmonary artery flow from a mean baseline of 37.7%. The study also found a 10.5-gram decrease in right ventricular mass from a mean baseline of 110.4 grams. And there was a 6.2-milliliter decrease in right ventricular end-diastolic volume from a mean baseline of 149.8 milliliters. There was also a mean increase in six-minute walking distance of 35.6 meters at Week 26 from a baseline of 411.2 meters.[1]

At Week 26, 57.1% of patients were in the improved category regarding WHO functional class, while the functional class for 43% of patients remained unchanged. No patients had worsened, and 1 patient had missing data. At baseline, 1 patient was in functional class I, 34 patients were in functional class II, and 35 patients were in functional class III.[1]

Dr. Young:
Thanks, Dr. Channick. What did the REPAIR study observe in terms of safety and tolerability?

Dr. Channick:
Safety and tolerability were assessed in 87 patients in the REPAIR study over a median exposure period of 52 weeks. Seventy-five patients, or 86.2% of the study population, reported at least one treatment-emergent adverse event. The most frequent adverse events that occurred in 10% or higher were peripheral edema, headache, dizziness, cough, a decrease in hemoglobin, upper respiratory tract infection, and myalgia. Seven patients, which was 8% of the study population, reported an adverse event that led to them discontinuing study treatment, including elevated aminotransferases and transaminases, increased hypersensitivity, increased liver function tests, and peripheral edema. Fourteen patients, which was 16.1% of the study population, reported at least one treatment-emergent serious adverse event including pneumonia, acute myocardial infarction, pulmonary arterial hypertension, pulmonary embolism, and sepsis. One death was reported as a result of a fatal cardiac arrest, which occurred after the patient experienced a pulmonary embolism.[1]

Dr. Young:
Thanks, Dr. Channick. I appreciate your insights on the REPAIR study, and I'm sure our listeners will as well.

And now before we wrap up for today, let's go over some Important Safety Information for OPSUMIT®.

Announcer:
Warnings and Precautions

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 the full Prescribing Information, including Boxed Warning, at www.opsumithcp.com.

Dr. Young:
I'd like to close our program today with a brief recap of the SERAPHIN pivotal trial we covered earlier, as well as the REPAIR study we've been discussing throughout today's program. Dr. Channick, would you be able to share a few key takeaways for our listeners?

Dr. Channick:
Sure. Thank you for asking. First, I'd like to remind our listeners that OPSUMIT® has a Boxed Warning for embryo-fetal toxicity, which you can find in the full Prescribing Information at www.opsumithcp.com. As we discussed previously, the FDA approved OPSUMIT ® in 2013 based on the efficacy and safety established in the pivotal SERAPHIN study.[8-9] SERAPHIN was the largest long-term outcomes-based pivotal trial of an endothelin receptor antagonist, or ERA, in PAH.[10] It included 742 patients with an average treatment duration of approximately 2 years. Compared with placebo, OPSUMIT® 10 milligrams was found to significantly reduce the risk of the first occurrence of a morbidity or mortality event by 45%.[8]

Following the SERAPHIN pivotal trial, we've since conducted other studies of OPSUMIT®. One of those is the REPAIR open-label study, which involved 87 patients taking OPSUMIT®. The open-label REPAIR study explored two primary endpoints, right ventricular stroke volume, as measured by cardiac magnetic resonance, and pulmonary vascular resistance, as measured by right heart catheterization.[1]

In the primary interim analysis of 42 study participants, the study found there was a 15.2-milliliter increase in right ventricular stroke volume and a 37% decrease in pulmonary vascular resistance at Week 26 over baseline. In the final analysis of 71 study participants, which was consistent with the primary interim analysis set, the study found there was a 12-milliliter increase in right ventricular stroke volume, and a 38% decrease in pulmonary vascular resistance at Week 26 over baseline.[1]

Treatment-emergent adverse events observed in at least 10% of patients in the safety set of the REPAIR study included peripheral edema in 21.8%, headache in 20.7%, dizziness in 13.8%, cough in 11.5%, decreased hemoglobin in 11.5%, upper respiratory tract infection in 11.5%, and myalgia in 10.3%. The overall incidence of treatment discontinuation due to adverse events was approximately 7%. And finally, one death was reported as a result of a fatal cardiac arrest, which occurred after the patient experienced a pulmonary embolism.[1]

Dr. Young:
Thanks so much for that summary. And thanks for joining us today. Dr. Channick.

Dr. Channick:
My pleasure being here.

Announcer:
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