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info@reachmd.com
(866) 423-7849

Efficacy and Safety of Macitentan Tadalafil Fixed Dose Combination in Pulmonary Arterial Hypertension: Results From the Phase III A DUE Study

Announcer:
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Dr. Chin:
Hi, this is Kelly Chin from UT Southwestern in Dallas, Texas, presenting the results of the A DUE study, efficacy, and safety of macitentan tadalafil fixed-dose combination in pulmonary arterial hypertension.

In Group 1 PAH, guidelines recommend combination therapy for most patients with PAH, in particular, the combination of a phosphodiesterase type 5 inhibitor and an endothelin-1 receptor antagonist. The fixed-dose combination of macitentan 10 milligrams and tadalafil 40 milligrams as a single tablet combination therapy would offer a simplified treatment approach. The A DUE study sought to evaluate the efficacy and safety of this approach.

Patients in the study were required to be functional class II or III, and either treatment-naive or a stable dose of background therapy with either an ERA or a PDE5 inhibitor. For patients who were treatment-naïve, they were randomized in a 1:2:1 fashion to macitentan 10 milligrams, fixed-dose combination therapy with both medications, or tadalafil 40 milligrams. For those on a prior endothelin receptor antagonist, they were randomized to macitentan 10 milligrams or the fixed-dose combination. And for those on a prior PDE5 inhibitor, they were randomized to tadalafil 40 milligrams, or the fixed-dose combination in the ratio shown at the top.

This resulted in the numbers at the bottom right, 35 macitentan patients, 108 macitentan/tadalafil fixed-dose combination, and 44 tadalafil. Because we were interested in analyzing the fixed-dose combination versus each monotherapy separately, two separate comparisons were performed. For the macitentan comparison, the fixed-dose comparator was only those patients on a prior ERA, or who were treatment naive, as shown here at the bottom. For those in - for the tadalafil comparison, the fixed-dose combination comparator was patients who are either treatment naive or those on a prior PDE5, as shown here. And as data, the primary endpoint was changed in PVR, expressed as a ratio of baseline at 16 weeks. The first hierarchical secondary endpoint tested was changed in 6-minute walk, and safety and tolerability were monitored throughout.

The demographics and baseline characteristics are shown here. As with most PAH studies, a majority of patients were female, and the mean age was around 50 years. The patient population was split between function class II and III, and hemodynamically, the elevation in PVR was quite high with an average PVR above 800 dynes, or more than 10 Wood units. For the primary endpoint, the reduction in PVR seen at 16 weeks in the macitentan comparison group for the fixed-dose combination was 45%, and for macitentan was 23%. For the comparison versus tadalafil, the fixed-dose combination group had a 44% decline in PVR, versus the 22% decline for tadalafil. This was highly significant, analyzed as a ratio, and with the P-values shown, these P-values are adjusted P-values for the multiple

comparisons with two different comparisons as well as one interim analysis that was performed after the first 100 patients were enrolled.

For a 6-minute walk distance, there was no statistically significant difference in the two groups. However, there was a very large improvement in the fixed-dose combination arms with a 53% improvement on the comparator versus macitentan, and a 43-meter improvement for the comparator versus tadalafil. This resulted in a between-group difference of 16 meters versus macitentan and 25 meters versus tadalafil. And this approached statistical significance.

Although these did not reach the predefined statistical significance level, these are large improvements and clinically potentially meaningful. The study was also not powered to detect a change in 6-minute walk distance with a substantially larger patient population needed when using an active comparator, as was done in this study.

From a safety and tolerability standpoint, there was a generally expected AE profile based on already-known side effects with either tadalafil or macitentan. And as expected, there were more treatment-emergent AEs with the combination therapy versus either monotherapy. This is often seen because you're using two medications at full dose, and so we do see slightly higher AE rates. Most of these were not serious, but there was a higher rate of serious adverse events as well. And AEs of special interest included anemia, which has been associated with ERA use, in macitentan in particular, this was seen at a higher rate in the fixed-dose combination group. And then also hypotension which is not generally seen with either therapy as monotherapy but we do know that the more PAH therapies used together, the more likely we are to see lower blood pressure. For most patients, this was mild and did not require treatment discontinuation.

In summary, the A DUE study met its primary endpoint, fixed-dose combination therapy with macitentan and tadalafil, led to a highly significant and marked improvement in PVR versus macitentan or tadalafil monotherapy. A trend for clinically relevant improvement in 6-minute walk distance was also seen in favor of the fixed-dose combination therapy, but this did not reach statistical significance. The safety profile of combination therapy was consistent with the safety profile of the individual medications, but we did see a higher overall a rate. Overall, A DUE supports macitentan/tadalafil fixed-dose combination, potentially as a single tablet for initial dual combination therapy in PAH.

So thank you, and I appreciate your attention.

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