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Imatinib for Group 1 PAH

Announcer:
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Dr. Shlobin:
My name is Oksana Shlobin. I'm a Medical Director of the Pulmonary Hypertension Program at Inova Fairfax Hospital, and today I'm going to talk to you about imatinib for Group 1 pulmonary arterial hypertension.

Imatinib is an antiproliferative tyrosine kinase inhibitor with a unique mechanism of action. Originally, it was developed for patients with chronic myeloid leukemia. It inhibits PDGF receptors, alpha and beta, as well as KIT, DDR, CSF1R, and ABL, and some of them have been implicated in pulmonary arterial hypertension. Imatinib has been studied in experimental models of pulmonary hypertension, as well as animal models, and were shown to have pulmonary vasodilatory effects and also proapoptotic effects in both of those scenarios. A randomized, double-blind, placebo-controlled phase 2 study in 59 patients with PAH reported that imatinib significantly improved pulmonary hemodynamics.

So let's talk about phase 3 IMPRES trial of oral imatinib. It enrolled patients with functional class II to IV who were on at least two background therapies and looked at 6-minute walk test distance difference in patients who were treated with oral imatinib, in comparison to baseline. Patients who were on the drug had a 32-meter placebo-controlled difference. And the data was also supported by multiple hemodynamic parameters, including mean PA pressure, cardiac output, pulmonary vascular resistance, and right atrial pressure.

There is a new formulation of inhaled imatinib, which is AV-101. It's an inhaled powder formulation with the thought that direct delivery to the lungs limits systemic exposure and avoids some of the gastrointestinal side effects of the oral drug. It is dosed as two capsules twice a day via a CDA inhaler. And phase 1 trials in healthy volunteers showed both safety and tolerability with no serious adverse effects reported, included some of the parameters in pulmonary function. The most common side effect was cough.

IMPAHCT is a study of inhaled imatinib, and it uses adaptive continuous trial design, with the phase 2B intermediate phase and phase 3 trials. Phase 2B trial uses 3:1 randomization of different doses, three different doses and placebo, and it is a 24-week study. As the study is completed and data is analyzed, an intermediate phase trial with the same randomization starts recruiting patients. And once phase 2B trial shows an optimal dosing, patients in the intermediate phase are all switched to the optimal dose, other than placebo patients. At the same time, phase 3 trial starts enrolling patients, half of them would be on optimal dose and half of them would be on placebo. Both intermediate phase and phase 3 trials are 24 weeks each, and then they are analyzed as a group for primary endpoint being change in 6-minutes walk test distance.

The inclusion criteria for this trial are typical to what we see for patients – for, sorry - for trials with pulmonary arterial hypertension. The primary endpoints are different. So phase 2B trial has change in pulmonary vascular resistance, and phase 3 trial has changed in 6-minute walk test distance. Both are 24 weeks as their primary endpoint. There is an exclusion criteria of patients who are on anticoagulants and antiplatelet therapy, and inhaled prostacyclins.

The key secondary and exploratory endpoints are shown here on the slide. And for phase 2B and phase 3, some of them are similar, and there are a couple of them that are different. The different endpoints for phase 2B is a change from baseline at week 24 of 6-minute walk test distance, NT-proBNP, and hemodynamics. And for phase 3, the hemodynamics are not measured, and 6-minute walk test distance is a primary endpoint. Phase 2B trial looks at incidence of clinical worsening events, and phase 3 trial looks at time to clinical worsening events. The exploratory endpoint looks at echo RV data.

In summary, inhaled imatinib is going to be looked at in phase 2B and phase 3 trial, and we're looking forward to the results.

Thank you so much.

Announcer:
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