Sitaxsentan Proves Effective in Pulmonary Arterial Hypertension

The phase III trial found that the 100-mg dose improved WHO functional class vs. placebo.

BY BRUCE GOLDMAN
Contributing Writer

SAN DIEGO — An investigational drug, sitaxsentan, improved exercise capacity and World Health Organization functional class in patients with pulmonary arterial hypertension in a phase III trial, Robyn J. Barst, M.D., reported at the 100th International Conference of the American Thoracic Society.

The drug also exhibited a favorable safety profile.

STRIDE-2 (Sitaxsentan to Relieve Impaired Exercise) was a 246-patient, 18-week, randomized, double-blind, placebo-controlled clinical trial of sitaxsentan, which is in development by Encysive Pharmaceuticals under the trade name Thelin.

"STRIDE-2 confirmed what its predecessor, STRIDE-1, showed: Sitaxsentan at 100 mg is safe and efficacious, with a low incidence of acute hepatotoxicity," said Dr. Barst, professor of pediatrics at Columbia University, New York, and director of New York Presbyterian Hospital's Pulmonary Hypertension Center.

In the study, conducted at 55 centers around the world, about 60 patients were randomized to once-daily oral doses of 50 mg or 100 mg of sitaxsentan or placebo. An additional 60 patients received twice-daily, open-label doses of bosentan (Tracleer, marketed by Actelion Pharmaceuticals), the only currently approved oral medication for pulmonary arterial hypertension (PAH).

PAH is uncommon, affecting an estimated 100,000-200,000 people worldwide, but the prevalence is rising with the advent of noninvasive diagnostic methods and improved treatment. Relentlessly progressive, the disease is characterized by high blood pressure and extensive remodeling of pulmonary arterial walls. Without lung or heart/lung transplantation, PAH is inevitably fatal, with a median survival of about 2.8 years.

One of the hallmarks of PAH is a high level of endothelin in the pulmonary vasculature. Endothelin is a potent mediator of both blood-vessel constriction and smooth-muscle proliferation. Two endothelin receptor subtypes, designated ET-A and ET-B, reside on pulmonary endothelial and smooth-muscle cells.

Animal and human studies have suggested that, whereas ET-A is strongly implicated in the etiology of PAH, ET-B's role may be beneficial, and therefore that a selective ET-A blocker might be desirable. Bosentan blocks both receptor types, while sitaxsentan is extremely selective for ET-A, Dr. Barst said.

Moreover, bosentan has been associated with relatively high rates of liver function abnormalities. Sitaxsentan has oral bioavailability exceeding 90% and a relatively long duration of action, permitting dosing on a once-a-day basis, she said.

In the 6-minute walk, the primary end point in STRIDE-2, the sitaxsentan 100-mg group had a statistically significant increase of 31.4 meters over placebo, with open-label bosentan increasing the distance by 29.5 meters over placebo. Among patients on the 100-mg sitaxsentan dose, the 6-minute walk distance appeared on average to continue improving after week 12; bosentan's efficacy appeared to peak at week 12 and then trend downward.

At 100 mg, sitaxsentan 'is safe and efficacious, with a low incidence of acute hepatotoxicity.'

DR. BARST

Sitaxsentan at 100 mg, but not open-label bosentan, improved World Health Organization functional class versus placebo. Sitaxsentan at 100 mg, but not at 50 mg, trended toward clinical significance in delaying clinical worsening, Dr. Barst reported.

At 18 weeks, the 100-mg sitaxsentan dose was associated with a 3% rate of liver function abnormality (liver enzyme elevations to greater than three times the upper limit of normal), compared with 6% for placebo and 11% for bosentan. Liver enzyme abnormalities reversed in all cases. These results are consistent with earlier studies of the two drugs and with bosentan's package insert. Other adverse effects of sitaxsentan didn't appear to have high clinical significance, she said.

About 72% of STRIDE-2 subjects were on warfarin, a blood-thinning agent commonly prescribed for PAH patients. Sitaxsentan inhibits, and bosentan enhances, the metabolism of warfarin, the levels of which must therefore be monitored and in many cases decreased when sitaxsentan is coadministered.

In this trial, bosentan necessitated about the same number of per-patient warfarin dose adjustments as did sitaxsentan, but in the opposite direction, Dr. Barst reported. ■

Sitaxsentan Better Tolerated Than Bosentan as Oral PAH Therapy

BY BRUCE GOLDMAN
Contributing Writer

SAN DIEGO — The investigational drug sitaxsentan was safe and effective for treating pulmonary arterial hypertension in a study of 48 patients for whom the only currently approved oral therapy, bosentan, was ineffective or toxic.

The findings suggest that "patients who are getting a good therapeutic benefit from an endothelin antagonist, but are having problems with liver toxicity on bosentan, can be safely changed to sitaxsentan with a low likelihood of recurrence, and thereby still get the benefit of an endothelin antagonist," Raymond Benza, M.D., said at the 100th International Conference of the American Thoracic Society.

Both bosentan and sitaxsentan are orally administered endothelin-receptor antagonists, but bosentan blocks both the "A" and "B" receptor subtypes, whereas sitaxsentan is highly selective for the A subtype. Unlike twice-daily bosentan, sitaxsentan can be given once daily because it is metabolized differently and has a longer duration of action, said Dr. Benza of the University of Alabama, Birmingham.

All patients in the randomized, double-blind, multicenter trial, called STRIDE-6, either had idiopathic (primary) pulmonary arterial hypertension (PAH) or had developed the syndrome as a consequence of having either connective tissue disease or congenital heart disease.

Overall, 35 of the patients in the study had discontinued bosentan because of an inadequate clinical response (the "efficacy subset"). The other 13 patients had discontinued bosentan therapy because of safety issues (the "safety subset"), 1 because of a rash, and 12 because of liver toxicity (liver enzyme elevations to greater than three times the upper limit of normal). Liver toxicity historically occurs in 10%-15% of patients treated with bosentan.

Patients in each of the two subsets were randomized to 50 mg or 100 mg of sitaxsentan and tested 12 weeks later for changes in 6-minute walk distance, WHO functional class (an index of severity), and Borg dyspnea score (a measure of breathing difficulty).

At the trial's end, 5 of the 15 subjects on the 100-mg sitaxsentan dose in the efficacy subset showed at least 15% improvements in 6-minute walk distance, with similar results for the other two efficacy criteria. (The 50-mg dose had lower efficacy.) In total, five patients in the efficacy subset dropped out of the study before its completion. None of the 35 patients in this subset experienced any liver toxicity on sitaxsentan.

All 13 patients in the safety subset (4 on 50 mg and 9 on 100 mg of sitaxsentan) completed the study, and 12 had no recurrence of their toxicity after being placed on sitaxsentan. None showed significant deterioration in their clinical condition. A single patient, who had developed liver toxicity after 1 month on bosentan and again on bosentan rechallenge after a 4-week interruption, experienced elevated liver enzymes during week 12 of therapy with 100 mg of sitaxsentan. The liver enzyme elevation subsided after sitaxsentan therapy was stopped.

Encysive Pharmaceuticals has since filed a New Drug Application with the Food and Drug Administration for approval of the 100-mg dose of sitaxsentan, under the trade name Thelin, as a first-line oral therapy for PAH. ■

First Inhaled Drug for PAH Approved

The Food and Drug administration approved the first inhaled therapy for pulmonary arterial hypertension.

Iloprost, a stable synthetic analogue of prostacyclin, causes selective pulmonary vasodilation, improving exercise capacity and hemodynamics in patients with PAH.

The drug is a strong vasodilator and inhibitor of platelet aggregation. The inhalation formulation (Ventavis Inhalant Solution) was developed to replace continuous infusion prostacyclin, which was the first therapy shown to reduce mortality in a controlled study of patients with severe pulmonary hypertension. In nature, prostacyclin is a local hormone; intravenous introduction can result in systemic side effects and progressive tolerance, requiring more and more of the drug.

The randomized clinical trial reported for approval was conducted on 203 adult patients with PAH; 101 received inhaled iloprost, and 102 received placebo. The response rate in the iloprost group (6-9 inhalations per day) was 19%, compared with 4% for the placebo group. The response rate was determined using a primary composite end point that incorporated improvement in exercise capacity, improvement in at least one New York Heart Association PAH class, and no death or deterioration. Adverse responses with iloprost included flushing, cough, jaw pain, and headache.

Iloprost is dispensed in single-use glass ampules (2 mL) containing 20 mcg iloprost for inhalation via the Prodose Adaptive Aerosol Delivery system. Labeling indicated that iloprost should not be inhaled more than once every 2 hours, and the drug is not effective while a patient is sleeping. Vital signs should be monitored when initiating iloprost because of the risk of syncope.

Iloprost, though not yet commercially available in the United States, will be marketed by CoTherix Inc. as the Ventavis Inhalant Solution under exclusive contract with Schering AG, which markets the drug in Europe and Australia.

CoTherix had previously received orphan drug designation for iloprost from the FDA, in August 2004.

Iloprost is also undergoing continuing clinical trials in the United States to examine its interaction with other drug treatments for PAH, as well as for its potential as a preventive agent for lung cancer in heavy smokers.

—Mark S. Lesney