Selexipag is an oral nonprostanoid diphenylpyrazine derivative that binds the prostaglandin I_2 (IP) receptor with high affinity. The active metabolite of selexipag has a prolonged half-life in comparison with prostanoid analogues and permits twice-daily dosing. The efficacy of selexipag was evaluated in patients with PAH in New York Heart Association (NYHA) FC II to III on background therapy with either an endothelin-1 (ET-1) receptor antagonist or sildenafil, or both. This trial represents the largest randomized placebo-controlled trial among patients with PAH ever completed, enrolling 1156 patients treated for a median of 1.4 years. Selexipag reduced the risk of hospitalization and the risk of disease progression by 43% ($p < .0001$) compared to those who received placebo. There were no significant differences in mortality between the two study groups, and the side effect profile was similar to that of prostacyclins.

Endothelin Receptor Antagonists Endothelin receptor antagonists (ERAs) inhibit the detrimental effects of ET-1, a potent endogenous vasoconstrictor and vascular smooth muscle mitogen. In PAH, ET-1 associates positively with PVR and mPAP, and inversely with CO and 6-MWD. The ET-1 signaling axis is complex and cell type–specific: ET type A (ET_A) and type B (ET_B) receptors expressed in pulmonary artery smooth muscle cells mediate vasoconstriction, whereas human pulmonary artery endothelial cells express ET_B receptors that promote ET-1 clearance and vasodilation through endothelial nitric oxide synthase activation and prostacyclin release.

The three ERAs approved for use in the United States are the nonselective $ET_{A/B}$ receptor antagonists bosentan and macitentan and the selective ET_A antagonist ambrisentan. Studies have shown that bosentan improves hemodynamics and exercise capacity and delays clinical worsening. The randomized, placebo-controlled, phase 3 Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 trial comparing bosentan to placebo demonstrated improved symptoms, 6-MWD, and WHO FC in patients treated with bosentan. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients