

Sitaxsentan, a Selective Endothelin-A Receptor Antagonist, Improves Exercise Capacity in PAH Associated With CTD

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ABSTRACT

Objectives: Pulmonary arterial hypertension (PAH) is a leading cause of death and late disease morbidity in connective tissue disease (CTD) and is generally regarded as less responsive to therapy than other forms of PAH, particularly in the setting of systemic sclerosis (SSc). Endothelin levels are increased in SSc-PAH and have vasoconstrictive effects mediated predominantly via the endothelin-A receptor (ET_A). Sitaxsentan is a once daily, orally bioavailable, highly selective (6500:1 - A:B) antagonist of the ET_A receptor. We investigated its clinical efficacy in PAH-CTD via analysis of all currently completed sitaxsentan placebo-controlled clinical trials in PAH.

Methods: Three multicenter, randomized, double-blind, placebo controlled trials of PAH including WHO Class II, III and IV have been completed (STRIDE -1, 2 & 4). Studies were of 12-18 weeks duration and six minute walk distance (6MWD) was the primary or secondary outcome in all. Studies included sitaxsentan at 50 mg, 100 mg and 300 mg once daily (QD). 110 of 512 patients had PAH-CTD including 63 with SSc, 22 with overlap/mixed connective tissue disease (MCTD) and 25 with systemic lupus erythematosus (SLE). All studies excluded patients with total lung capacity <80% predicted or baseline 6MWD >450 m (2 of 3 studies). These trials also included idiopathic PAH (IPAH) and PAH associated with congenital heart defects.

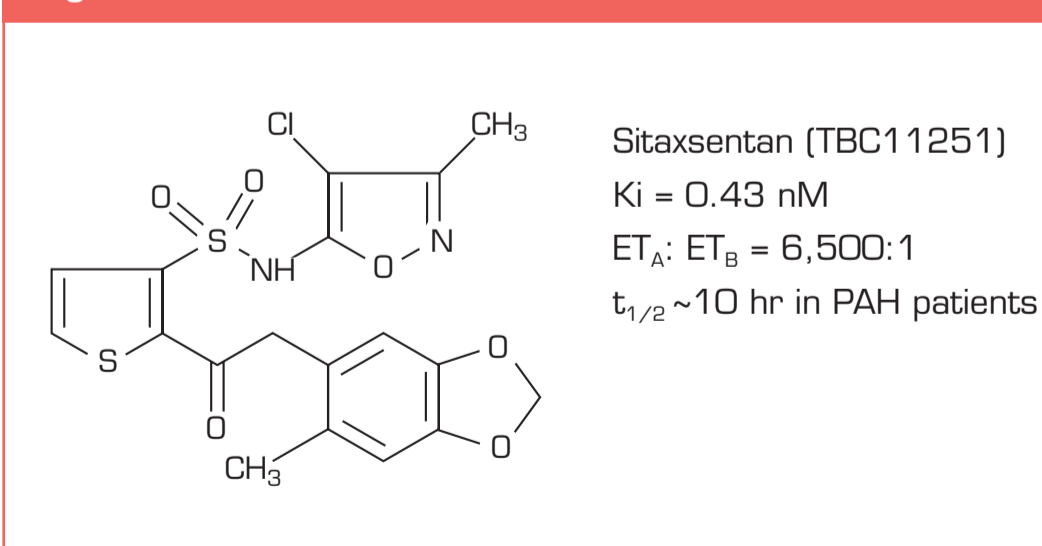
Table. Six Minute Walk Distance (m)				
	Placebo (PBO) N = 28	Sitax 50 mg N = 26	Sitax 100 mg N = 39	Sitax 300 mg N = 17
Δ from Baseline (mean ± SE)	-16 ± 15.0	-2 ± 13.4	21 ± 10.4	2 ± 14.1
PBO-subtracted treatment effect		14.7	37.7	18.3
P-value vs PBO		NS	P = 0.042	NS
N (%) Abnormal LFT >3× ULN	1 (3.6%)	0 (0%)	0 (0%)	0 (0%)

Conclusion: Sitaxsentan 100 mg improves 6MWD in patients with PAH-CTD with a low incidence of abnormal liver function tests. Selective ET_A receptor antagonism appears to be an effective and well-tolerated therapy for PAH associated with CTD.

INTRODUCTION

- Pulmonary arterial hypertension (PAH) is a serious, progressive, and difficult to manage condition that causes high blood pressure in the pulmonary artery¹
- PAH is a leading cause of death and late disease morbidity in connective tissue disease (CTD) such as scleroderma, mixed CTD (MCTD) (overlap syndromes), and systemic lupus erythematosus (SLE)²
- The incidence of PAH in scleroderma and SLE is 12%-33% and 6.2%-14%, respectively²
- PAH in CTD appears to be less responsive to therapy than other forms of PAH, possibly due to late recognition, an older patient population with comorbidities, more severe structural changes in the pulmonary vasculature, diminished right ventricular reserve, or concomitant diseases such as parenchymal lung disease, left ventricular diastolic disease, or pulmonary veno-occlusive disease²⁻⁴
- Immunohistochemistry of control and systematic sclerosis (SSc) lung samples demonstrated increased endothelin-1 (ET-1) levels in SSc-PAH⁵
- Blocking ET_A receptors appears to improve the symptoms of PAH⁶
- Sitaxsentan is a once-daily, orally bioavailable, highly selective ET_A (6500:1 ET_A:ET_B) receptor antagonist (Figure 1)^{7,8}

Figure 1. Sitaxsentan



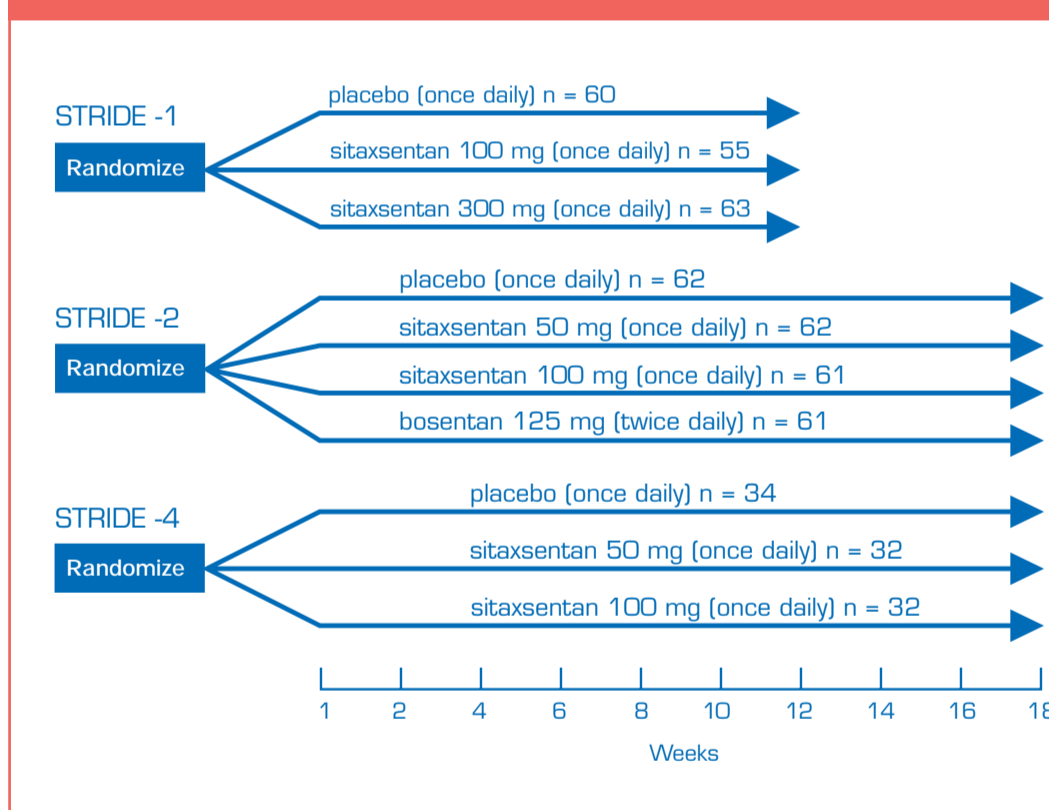
OBJECTIVES

- To evaluate the clinical efficacy of sitaxsentan in PAH associated with CTD using the 3 completed, multicenter, randomized, double-blind, placebo-controlled clinical trials (Sitaxsentan To Relieve Impaired Exercise [STRIDE]-1, STRIDE-2, and STRIDE-4). 6MWD was the primary outcome measure

METHODS

- STRIDE-1, STRIDE-2, and STRIDE-4 were double-blind, placebo-controlled clinical trials that included patients with idiopathic PAH (IPAH), PAH associated with congenital heart defects (PAH-CHD), and PAH-CTD (Figure 2)

Figure 2. Study Designs of STRIDE-1, STRIDE-2, and STRIDE-4



- PAH-CTD patients in WHO/NYHA functional classes II-IV from the STRIDE-1, STRIDE-2, and STRIDE-4 studies were included in this combined analysis
- Changes in 6MWD were assessed in untreated PAH-CTD patients (n = 28) and compared with 82 patients receiving sitaxsentan at 50, 100, and 300 mg once daily (QD)
- The patient population included individuals with SSc (n = 63), overlap mixed connective tissue disease (overlap/MCTD) (n = 22), or SLE (n = 25)
- The study duration was 12 weeks (STRIDE-1) or 18 weeks (STRIDE-2 and STRIDE-4)
- Studies excluded patients with
 - Total lung capacity <60% predicted
 - Total lung capacity of 60%-70% with high-resolution computed tomography showing more than mild interstitial lung disease
 - Baseline 6MWD >450 m (in 2 of 3 STRIDE studies)

RESULTS

- Sitaxsentan (100 mg) was found to increase the 6MWD by 21 ± 10.4 m above baseline over the 12-18 weeks of the study. In comparison, during the same period, the 6MWD of placebo-treated patients decreased by 16.0 ± 15.0 m, i.e., the placebo-subtracted treatment effect was 37.7 m (P = 0.042). No patient receiving sitaxsentan had elevated liver function tests (abLFT) defined as AST and/or ALT >3× ULN compared with 1 patient (3.6%) for placebo (Table 1)

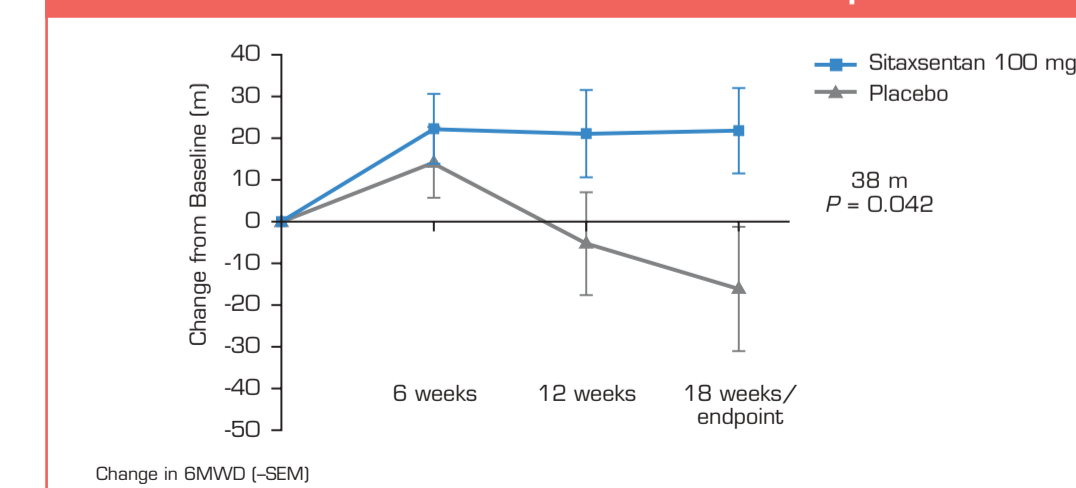
Table 1. 6MWD and Liver Enzyme Elevations

	Placebo n = 28	Sitaxsentan 50 mg n = 26	Sitaxsentan 100 mg n = 39	Sitaxsentan 300 mg n = 17
Change from baseline, m (mean ± SE)	-16 ± 15.0	-2 ± 13.4	21 ± 10.4	2 ± 14.1
Placebo-subtracted treatment effect		14.7	37.7	18.3
P value vs placebo		NS	P = 0.042	NS
AbLFT >3× ULN, n (%)	1 (3.6%)	0 (0%)	0 (0%)	0 (0%)

NS, nonsignificant; SE, standard error; ULN, upper limit of normal

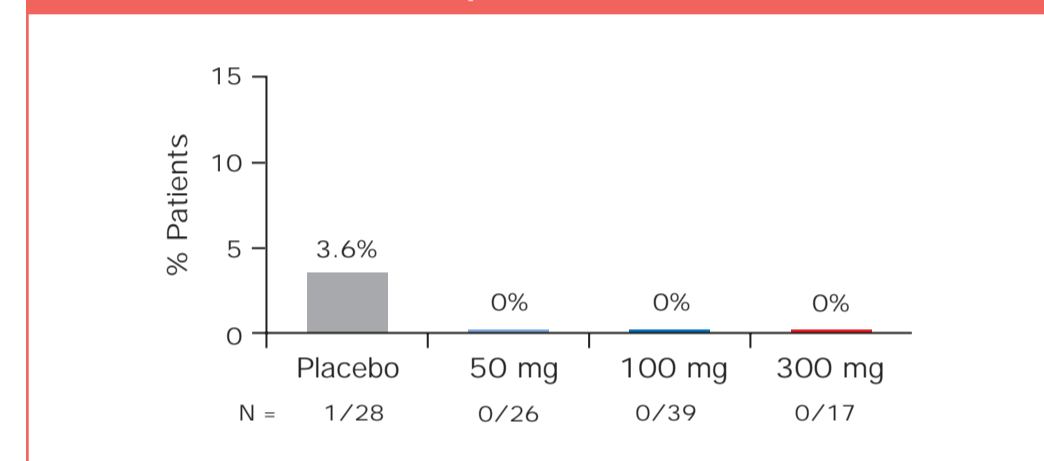
- Changes from baseline in 6MWD at 6, 12, and 18 weeks after the start of sitaxsentan 100 mg QD therapy in the PAH-CTD population are shown in Figure 3. Increases in 6MWD are noted as early as 6 weeks after the start of therapy with sitaxsentan and appear to remain constant through week 18. The declining function of the placebo group over time can be seen

Figure 3. Change in 6MWD (±SEM) From Baseline to End Point in the PAH-CTD Population



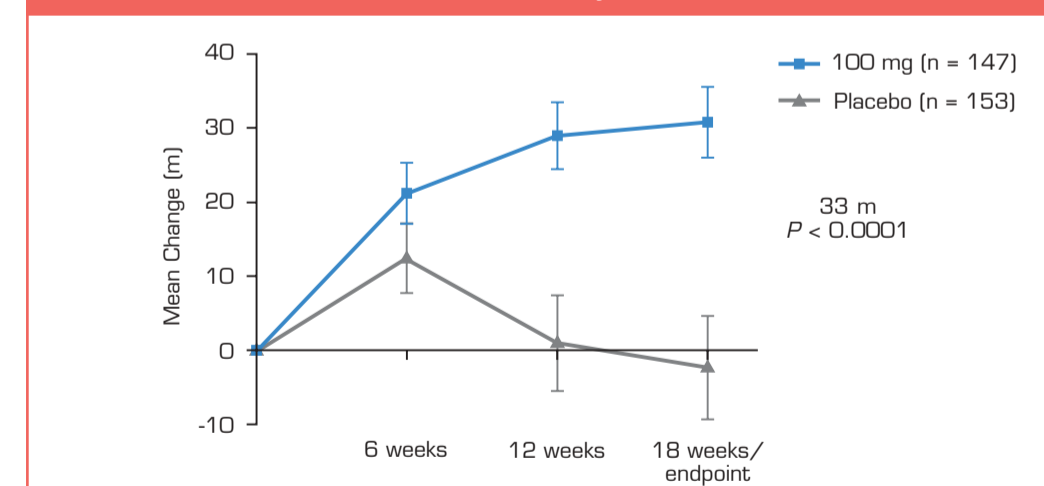
- Abnormal liver enzymes occurred in 3.6% of patients in the placebo group, but did not occur in any patient at any dose of sitaxsentan therapy during the 12-18 week trials (Figure 4)

Figure 4. Elevated Liver Enzymes >3× ULN in the PAH-CTD Population



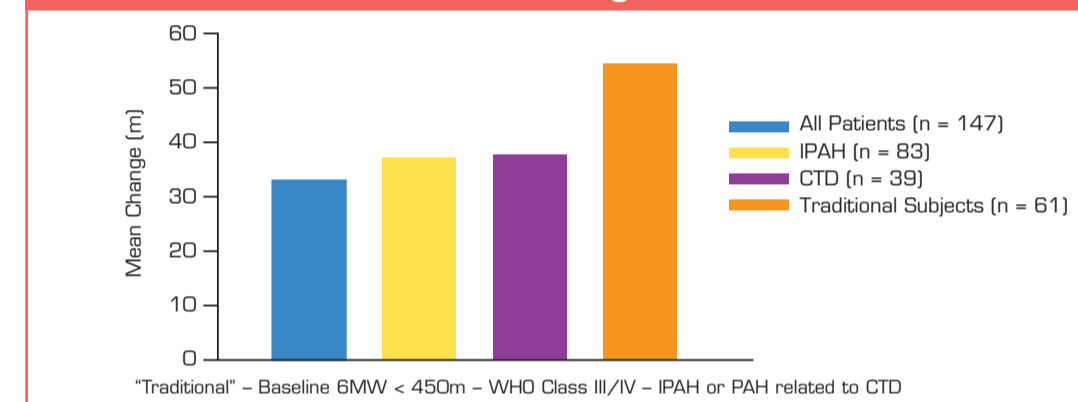
- Figure 5 shows that the 6MWD increased by 30.7 ± 4.7 m from baseline to end point (mean ± standard error of the mean [SEM]) in all PAH patients in the STRIDE-1, STRIDE-2, and STRIDE-4 trials treated with 100 mg QD of sitaxsentan (N = 147). By contrast, the placebo group of patients (N = 153) from these studies showed a 2.5 ± 6.7 m decrease in 6MWD (P < 0.01)

Figure 5. STRIDE-1, STRIDE-2, and STRIDE-4: 6MWD (± SEM) for All Subjects



- The mean change from baseline to end point in 6MWD was analyzed as a function of disease diagnosis (Figure 6). Results in the matched placebo group were subtracted from the sitaxsentan-treated group to obtain the mean difference. IPAH patients experienced a 37.2 m increase in 6MWD (95% CI = 14.7, 59.8; P = 0.0017). PAH-CTD patients had a 37.7 m increase in 6MWD (95% CI = 2.5, 73.0; P = 0.042). WHO class III/IV patients showed a 45.6 m increase in 6MWD (95% CI = 22.6, 68.5; P < 0.0001). In contrast, traditional subjects experienced a 54.6 m increase in 6MWD (95% CI = 25.5, 83.8; P < 0.0001). Traditional PAH patients are defined as: NYHA class III-IV, baseline 6MWD ≤ 450 m, and baseline diagnosis of IPAH or PAH-CTD.⁹

Figure 6. Placebo-Subtracted Change in 6MWD From Baseline to End Point by Subset (Sitaxsentan 100 mg)



- The 300 mg dose is considered efficacious; however, due to its higher incidence of abLFTs, further clinical development was limited to the 100 mg dose and exploratory at the 50 mg dose

CONCLUSIONS

- Sitaxsentan, a highly selective, oral, once-daily ET_A receptor antagonist, is a safe and effective treatment for PAH at a dose of 100 mg orally once daily
- Sitaxsentan 100 mg improves 6MWD in patients with PAH-CTD
- No patient receiving sitaxsentan experienced liver transaminase elevations during the 12-18 week trials
- Selective ET_A receptor antagonism with sitaxsentan seems to be an effective and well-tolerated therapy for PAH associated with CTD
- The present data support endothelin antagonism in the treatment of PAH-CTD

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