Combined Analysis of Outcomes of Sitaxentan Treatment of Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

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Introduction

- Pulmonary arterial hypertension (PAH) is a leading cause of morbidity and mortality in individuals with connective tissue disease (CTD). In PAH, endothelin (ET)–1 is a key vasoconstrictor (predominantly via endothelin-A [ET_A] receptors), and ET-receptor antagonists are established therapies. Sitaxentan sodium is a once-daily, orally bioavailable, highly selective (6500:1 ET_A vs ET_B) ET-receptor antagonist. In the European Union, it is approved for treatment in patients with World Health Organization Functional Class (WHO FC) III PAH.

Aim

- This report is a post hoc analysis of pooled data from the STRIDE (Sitaxentan To Relieve ImpaireD Exercise) 1, 2, and 4 trials. These were double-blind, randomized, placebo-controlled trials of sitaxentan use in patients aged 12–75 years with WHO FC II–IV idiopathic PAH or PAH associated with CTD (PAH-CTD) or congenital heart disease. The aim of this analysis is to describe the efficacy and safety of oral sitaxentan 100 mg once daily (QD; the currently approved dose) vs bosentan 125 mg twice daily (BID) and placebo in patients with PAH-CTD.

Methods

- Patients were randomized to sitaxentan 100 mg, sitaxentan 300 mg, or placebo QD for 12 weeks (STRIDE-1[1,2]); sitaxentan 50 mg, sitaxentan 100 mg, or placebo QD or open-label bosentan (62.5 mg followed by 125 mg) BID for 18 weeks (STRIDE-2[3]); and to sitaxentan 50 mg, sitaxentan 100 mg, or placebo QD for 18 weeks (STRIDE-4[4]).
- Efficacy endpoints included change from baseline in 6-minute walk distance (6MWD) and WHO FC and time to clinical worsening. Hemodynamic data were collected only in the STRIDE-1 study.
- Clinical worsening was defined as occurrence of any of the following events (a patient could have more than 1):
  - Hospitalization for worsening PAH
  - Death
  - Heart-lung or lung transplant
  - Atrial septostomy
  - Addition of any new chronic treatment for worsening PAH (ie, calcium channel blocker, digitalis, prostacyclin or prostacyclin analog, alternative ET-receptor antagonist, phosphodiesterase type 5 inhibitor, oxygen)
  - WHO FC deterioration plus ≥15% decrease in 6MWD from baseline
- Change in 6MWD and hemodynamic parameters were analyzed using a nonparametric analysis of covariance with treatment as a factor and baseline value as the covariate.
- Change in WHO FC was analyzed by a Cochran-Mantel-Haenszel mean score test controlled for baseline value, using modified ridit scores, which provided a *P* value for the distribution of the "improved," "no change," and "deterioration" categories across treatment groups.
- Time to clinical worsening was assessed by Kaplan-Meier estimation; *P* values of between-treatment comparisons were calculated based on the log-rank test.
- Safety endpoints included adverse events, discontinuation due to adverse events, and aspartate and/or alanine aminotransferase levels >3 times the upper limit of normal.
- Last observation carried forward was used for most outcomes. All analyses were post hoc with no adjustments for multiplicity.

Results

Population

- 86 patients with PAH-CTD were included, most of whom had systemic sclerosis (scleroderma; **Table 1**). Baseline characteristics were similar across the 3 trials and across the pooled treatment groups.

Table 1. Baseline Demographics and Characteristics in Patients With PAH-CTD

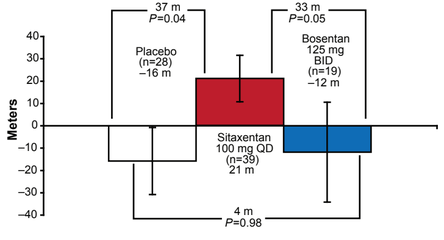
	Placebo (n=28)	Sitaxentan 100 mg QD (n=39)*	Bosentan 125 mg BID (n=19)
Mean ± SD age, y	50±16	56±12	52±15
Sex, n (%)			
Men	5 (18)	4 (10)	3 (16)
Women	23 (82)	35 (90)	16 (84)
Etiology of PAH-CTD, n (%)			
Systemic sclerosis (scleroderma)	13 (46)	19 (49)	10 (53)
Limited scleroderma	2 (7)	5 (13)	5 (26)
Mixed connective tissue diseases	3 (11)	6 (15)	2 (11)
Overlap syndrome	2 (7)	2 (5)	0
Systemic lupus erythematosus	8 (29)	7 (18)	2 (11)
Function			
WHO FC II/III/IV, n	9/18/1	14/24/1	8/11/0
Mean ± SD 6MWD, m	335.4±90.4	333.0±96.1	328.5±72.8
Mean ± SD pulmonary artery pressure, mmHg	45.8±11.9	42.5±10.4	43.2±13.0
Mean ± SD pulmonary capillary wedge pressure, mmHg	8.9±4.4	8.6±3.4	8.7±3.5
Mean ± SD pulmonary vascular resistance, mmHg/L/min	10.7±7.7	9.5±6.7	9.7±5.1

6MWD=6-min walk distance; PAH-CTD=pulmonary arterial hypertension associated with connective tissue disease; WHO FC=world health organization functional class.
*P>0.05 for all comparisons using analysis of variance (age, 6MWD, and hemodynamic variables) or Fisher exact test.

Observations on Treatment Effects

- The 6MWD increased in the sitaxentan group vs the placebo (P=0.04) and bosentan (P=0.05) groups **(Figure 1)**.

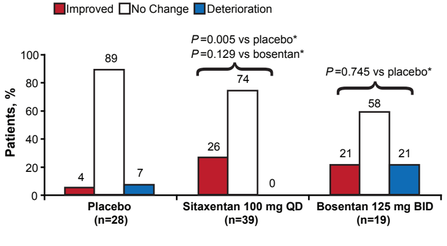
Figure 1. Mean ± SE Change From Baseline in 6-Minute Walk Distance in Patients With PAH-CTD



BID=twice daily; PAH-CTD=pulmonary arterial hypertension associated with connective tissue disease; QD=once daily.

- The change in WHO FC (distribution of the categories "improved," "no change," and "deterioration") differed significantly from placebo in the sitaxentan group (P=0.005) but not in the bosentan group **(Figure 2)**. In contrast to the other groups, none of the sitaxentan patients were in the "deterioration" category.

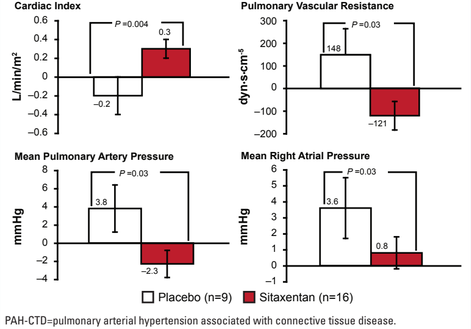
Figure 2. Effect on World Health Organization Functional Class in Patients With PAH-CTD



BID=twice daily; PAH-CTD=pulmonary arterial hypertension associated with connective tissue disease; QD=once daily.
*For distribution of the categories "improved," "no change," and "deterioration."

- In STRIDE-1, hemodynamic parameters showed improvement in the sitaxentan group vs placebo group (P<0.05; **Figure 3**).

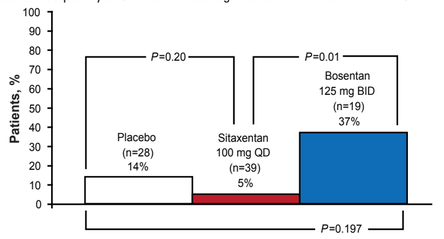
Figure 3. Mean ± SE Change From Baseline in Hemodynamics in Patients With PAH-CTD



PAH-CTD=pulmonary arterial hypertension associated with connective tissue disease.

- The frequency of clinical worsening events was significantly lower in the sitaxentan group vs bosentan group (P=0.01; **Figure 4**), and the time to clinical worsening was prolonged **(Figure 5)**.
- All therapies were well tolerated. The incidence of aspartate and/or alanine aminotransferase levels >3 times the upper limit of normal was 3% (placebo), 0% (sitaxentan), and 15% (bosentan). 3 patients discontinued because of adverse events (pancreatic pseudocyst [placebo], elevated liver function tests [bosentan], and exacerbation of PAH [bosentan]).

Figure 4. Frequency of Clinical Worsening Events in Patients With PAH-CTD

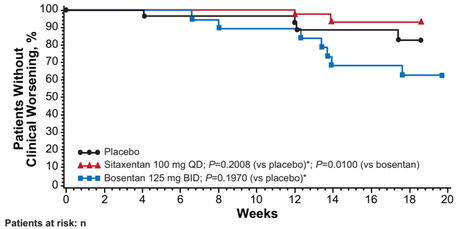


BID=twice daily; PAH-CTD=pulmonary arterial hypertension associated with connective tissue disease; QD=once daily.

Conclusions

- Sitaxentan 100 mg QD is an effective and well-tolerated therapy for patients with PAH-CTD.
  - 6MWD improved vs placebo and bosentan (P≤0.05).
  - No patient experienced a deterioration in WHO FC.
  - Hemodynamic parameters improved vs placebo (P<0.05).
  - Clinical worsening events were decreased in frequency and postponed vs bosentan (P=0.01).
- These findings appear to support the use of sitaxentan in patients with CTD-PAH but should be interpreted with caution because they are derived from post hoc analyses of short-term studies.
- A larger and longer prospective study is warranted.

Figure 5. Kaplan-Meier Estimate of the Time to Clinical Worsening in Patients With PAH-CTD



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