

One-Year Open-Label (OL) Comparison of Sitaxentan to Bosentan in Treatment of Pulmonary Arterial Hypertension (PAH) Related to Systemic Sclerosis (SSc)

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Abstract

Background: PAH is a leading cause of mortality and late disease morbidity in SSc and other CTDs. Short-term (12–18 week) randomized controlled trials (RCTs) in PAH studies (which included SSc patients) have demonstrated benefit in exercise capacity, functional status, hemodynamics, and quality of life in response to a variety of agents. Long-term controlled experiences are lacking; thus, data on clinically important measures such as survival and estimates of time to clinical worsening are by necessity derived from OL observational series.

Objectives: We examined multiple outcomes in patients with PAH related to SSc who were participants in a one-year OL observational study of sitaxentan and bosentan.

Methods: Sitaxentan is an orally bioavailable selective antagonist of the endothelin-A receptor. An 18-week RCT (STRIDE-2) compared sitaxentan 100 mg and 50 mg with placebo; an open-label bosentan (nonselective endothelin antagonist) arm was also included for observational comparisons only. The 18-week study was followed by a one-year OL study with sitaxentan 100 mg or bosentan (STRIDE-2X) (*Chest*. 2008;134:775-82). We report here post hoc subanalyses in those patients with diagnoses of SSc (n=49) treated with the recommended doses of each agent: sitaxentan 100 mg (n = 29) QD or bosentan 125 mg BID (n=20).

Results: The two treatment groups appeared comparable in terms of gender, age, WHO functional class, hemodynamics, and six minute walk distance prior to treatment initiation (322 m sitaxentan vs 308 m bosentan). **Table:**

	Outcomes at One Year, %		
	Sitaxentan	Bosentan	P Value
All discontinuations (D/C)	14	65	<0.001
D/C secondary increased AST/ALT	0	18	0.0229
Alive	97	75	0.023
Without clinical worsening	79	35	0.001

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Conclusion: As an OL observational experience following a RCT, there are significant potential study design limitations. One could speculate that bias was operative in both ways—either in favor of the novel agent or in favor of the approved drug. There are significant statistical limitations with OL data sets. Nonetheless, outcomes suggest increased efficacy and safety with sitaxentan. Importantly, this was the case in the longer-term robust outcomes of survival and ability to remain on monotherapy. However, it cannot be determined from clinical trial data such as these whether or not the present results with sitaxentan in PAH related to SSc are related to its selectivity for the endothelin-A receptor or if other factors are relevant.

Introduction

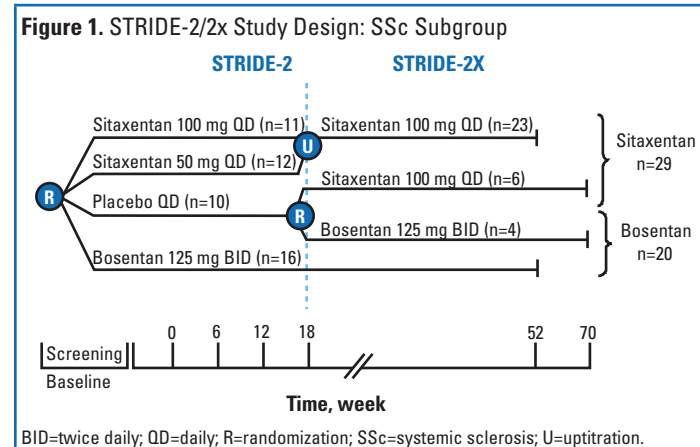
- Pulmonary arterial hypertension (PAH) is a leading cause of death and late disease morbidity in patients with systemic sclerosis (SSc, scleroderma).
- PAH occurs in 8%–12% of patients with connective tissue disease.^{1,2}
- In short-term (12–18 week) randomized controlled trials, patients with PAH secondary to SSc have demonstrated attenuated responses compared with patients with idiopathic PAH. This includes accepted outcome measures such as submaximal exercise testing (6-minute walk distance) and time to clinical worsening.^{3,4}
- Patients with PAH related to SSc remain in need of therapies with durable and important clinical effects.

Background

- Sitaxentan sodium (Thelin[®]) is an orally bioavailable, highly selective endothelin receptor antagonist (ETRA, 6500:1 ET_A:ET_B) licensed in the European Union, Canada, and Australia for the treatment of patients with PAH classified as World Health Organization (WHO) Functional Class III (and Class II in Canada).
- Endothelin-1 levels are increased in plasma and tissue of patients with SSc and have been implicated in vasospastic, vasoproliferative, fibrotic, and inflammatory features of illness.⁵

Methods

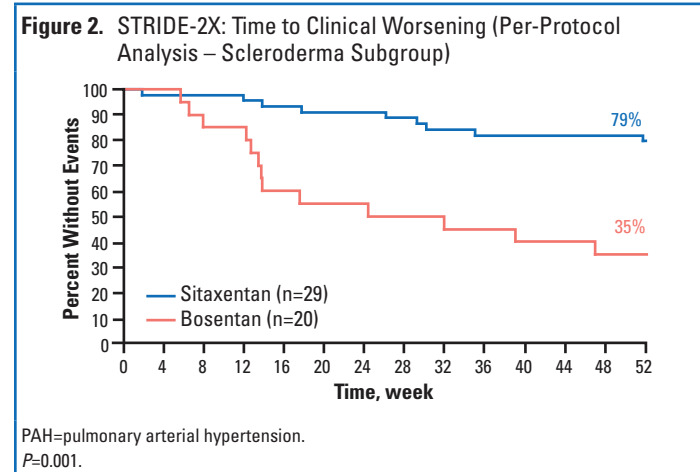
- Initial findings from the trial have been reported.⁶
- The first phase of the STRIDE-2 trial was double-blinded for the 2 doses of sitaxentan and placebo, whereas the bosentan arm was an open-label observational safety arm (**Figure 1**).
- STRIDE-2X was an open-label study (**Figure 1**).



- We performed a post hoc subgroup analysis of the 49 patients with SSc included in this trial, comprised of 29 patients receiving sitaxentan 100 mg once daily and 20 patients receiving bosentan 125 mg twice daily.
- Results are presented from the first date of exposure to sitaxentan 100 mg once daily and from the first date of exposure to bosentan 125 mg twice daily.

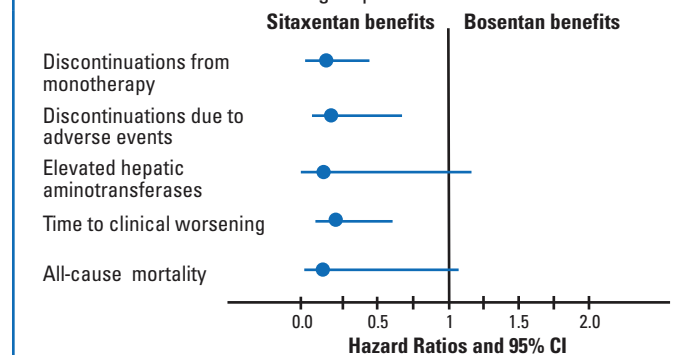
Results

- At 1 year, 79% of sitaxentan-treated and 35% of bosentan-treated patients did not experience clinical worsening (**Figure 2**).



- Clinical worsening was defined as death, hospitalization for PAH, treatment with any new PAH treatment, atrial septostomy, transplantation, or a combined decline in WHO functional class and $\geq 15\%$ decline in 6-minute walk distance from baseline.
- Patients treated with sitaxentan were able to remain on monotherapy for longer, demonstrated increased time to clinical worsening, and had increased survival compared with patients treated with bosentan (**Figure 3**).

Figure 3. Relative Risk Reduction at 1 Year for Sitaxentan Therapy in the Scleroderma Subgroup



Discussion

- Does selectivity matter?
 - Highly selective endothelin receptor antagonism
 - Reverses vasoconstriction⁷
 - Remodels pulmonary vasculature (hypoxic rat model)⁸
 - Allows ET_B to clear ET-1⁹
 - Allows ET_B to maintain nitric oxide and prostacyclin levels^{7,10}
 - Allows ET_B to maintain natriuretic effects, thus avoiding clinical edema¹¹
- Or are the present results a reflection of receptor antagonism pharmacology (**Table 1**)?
- This trial is limited by its open-label design and its primary intent of serving as an observational comparison of safety. This is a post hoc analysis.

Table 1. Pharmacologic Profiles of ETAs

	Sitaxentan ¹²	Bosentan ¹³	Ambrisentan ¹⁴
ET _A potency (K _i)	0.43 nM	4.1 nM	0.011 nM
ET _B potency (K _i)	>10 nM	343 nM	48.7 nM
ET _A :ET _B ratio	6500:1	20:1	>4000:1
t _{1/2} , h	10	5.4	9–15
Chronic systemic exposure	No accumulation at indicated dose	Reduced due to enzyme induction	Linear over 1–100 mg
Metabolized by	CYP3A4/2C9	CYP3A4/2C9	CYP3A4/2C19 and UGTs 1A9S, 2B7S, 1A3S
Effect on CYP	Inhibits CYP2C9 (2C8, 2C19, 3A4/5)	Inhibits CYP3A4, 2C9, 2C19	No information but caution advised
Elimination route	Renal/hepatic	Hepatic	Hepatic

CYP=cytochrome P450; ETRA=endothelin receptor antagonist; t_{1/2}=half-life; UGT=UDP-glucuronosyltransferases.

Conclusions

- The available ETAs (ambrisentan, bosentan, sitaxentan) have comparable effects on submaximal exercise capacity (6-minute walk distance) in patients with PAH secondary to SSc.³
- In this open-label observational experience, patients treated with sitaxentan were able to remain on monotherapy for longer, demonstrated increased time to clinical worsening, and had increased survival compared with patients treated with bosentan. Sitaxentan was well tolerated.

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