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Sitaxentan

In Pulmonary Arterial Hypertension

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Contents

Abstract

▲ Sitaxentan is a highly selective endothelin $(ET)_A$ receptor antagonist, with an ≈6500 higher affinity for ET_A than ET_B receptors. In pulmonary arterial hypertension (PAH), elevated ET-1 levels are strongly correlated with disease severity and prognosis.

▲ Sitaxentan 100mg once daily was efficacious in the management of moderate to severe PAH in the pivotal, 12–18 week, large (n ≥ 98), well designed, placebo-controlled STRIDE-1, -2 and -4 trials.

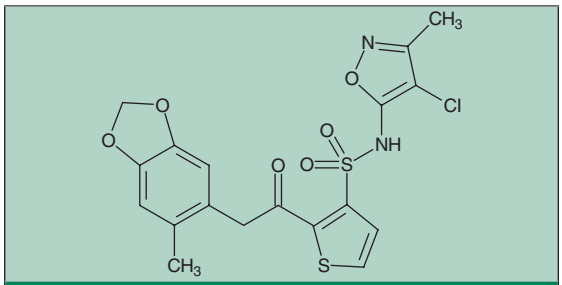
▲ In the STRIDE-1 and -2 trials (the majority of patients had New York Heart Association [NYHA]/WHO functional class III PAH), sitaxentan-treated patients experienced significantly greater improvements from baseline in distance walked over 6 minutes (6MWD; primary endpoint in STRIDE-2) and in NYHA/WHO functional class than placebo recipients.

▲ In STRIDE-4, although there was no between-group difference in terms of improvements in 6MWD in the primary analysis of patients across all WHO functional classes (61% were functional class II) [primary endpoint], improvements in 6MWD significantly favoured sitaxentan versus placebo-treated patients in a *post hoc* subgroup analysis of those with WHO functional class III or IV disease.

▲ The beneficial effects of sitaxentan therapy on exercise capacity and NYHA/WHO functional class were maintained after up to 2 years' treatment.

▲ Treatment with sitaxentan for up to 2 years was generally well tolerated in clinical trials.

Features and properties of sitaxentan (TBC 11251; IPI 1040; Thelin®)	
Indication	
For the improvement of exercise capacity in adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III. Efficacy has been shown in idiopathic PAH and in PAH associated with connective tissue disease	
Mechanism of action	
Highly selective endothelin $(ET)_A$ receptor antagonist	
Dosage and administration	
Route	Oral
Dose	100mg
Frequency	Once daily
Pharmacokinetic profile (oral sitaxentan 100mg steady-state mean values)	
Maximum plasma concentration	13 μg/mL
Trough plasma concentration	0.06 μg/mL
Area under the plasma concentration-time curve from zero to 24 hours	40 μg • h/mL
Terminal elimination half-life	10h
Most frequent treatment-related adverse events	
Headache, peripheral oedema, nasal congestion	



Sitaxentan

Current treatment options for the management of pulmonary arterial hypertension (PAH) focus on alleviating the symptoms of the disease, which typically include exertional breathlessness, chest pain and syncope.[1,2] PAH is a chronic disease defined by a mean pulmonary arterial pressure (MPAP) of >25mm Hg at rest and >30mm Hg during exercise and is characterised by a progressive increase in pulmonary vascular resistance (PVR), which ultimately leads to right ventricular failure and premature death.[3,4] In those with a diagnosis of idiopathic PAH, median life expectancy is <3 years if the disease is left untreated.[1]

The multifactorial mechanisms involved in the pathogenesis of PAH remain to be fully elucidated.[2] Nonetheless, four common factors are associated with the disease: vasoconstriction, pulmonary vascular proliferation, remodelling and thrombosis *in situ*.[2] A better understanding of the key role played by endothelial dysfunction and the chronic imbalance between vasoactive mediators (e.g. nitric oxide, prostacyclin and endothelin [ET]-1) that regulate pulmonary vascular tone has led to the development of new pharmacological approaches for the treatment of PAH.[2,5] These approaches include ET receptor antagonists (e.g. sitaxentan [Thelin®][1] and bosentan), synthetic prostacyclin and prostacyclin analogues (e.g. iloprost and epoprostenol), and phosphodiesterase-type 5 inhibitors (e.g. sildenafil).[5,6]

The role of dysregulation of ET in the pathogenesis of PAH is now firmly established.[2,5,7] ET-1, the major ET isoform, is primarily produced by vascular endothelial cells and has opposing actions depending on the location of the ET_A (expressed on pulmonary vascular smooth muscle cells [PVSMC]) and ET_B receptors (expressed on PVSMC and pulmonary endothelial cells) at which it binds.[7] Binding at ET_A and ET_B receptors located on PVSMC results in vasoconstriction and cellular proliferation, whereas binding at ET_B receptors on vascular endothelial cells is associated with vasodilation via stimulation of nitric oxide and prostacyclin synthesis.[7] Evidence of elevated ET levels in PAH patients also supports the role of ET, with a significant correlation between ET levels and disease severity and prognosis.[5] Further clinical experience is required to determine whether selective inhibition of the ET_A receptor (e.g. with sitaxentan) or nonselective inhibition of the ET_A and ET_B receptors (e.g. with bosentan) is the best pharmacological approach to ameliorate dysregulation of the ET system.[6,7]

This review focuses on the pharmacological and clinical profile of oral sitaxentan in patients with moderate to severe PAH.

1. Pharmacodynamic Profile

The pharmacodynamic properties of sitaxentan, a sulfonamide, have been evaluated in preclinical *in vitro* studies and animal models, and in patients with congestive heart failure. Data are supplemented with information from the European Medicines Agency (EMEA) summary of product characteristics.[8]

- Sitaxentan is a potent and highly selective ET_A receptor antagonist, with an approximately 6500-fold higher affinity for ET_A than ET_B receptors (the concentration required to inhibit 50% of activity was 1.4 vs 9800 nmol/L).[9] The inhibitory constant for the ET_A receptor was 0.43 nmol/L.
- The most common metabolites of sitaxentan have no clinically relevant pharmacological activity,[10] showing ≥10 times less activity than the parent drug.[8]
- In an animal model of chronic hypoxia-induced pulmonary hypertension, oral sitaxentan treatment

1 The use of trade names is for product identification purposes only and does not imply endorsement.

prevented or reversed the condition (reviewed by Wu et al.[9]). In spontaneously hypertensive hamsters, 7 weeks' treatment with oral sitaxentan significantly decreased systolic blood pressure from baseline levels (109 vs 175mm Hg at baseline; $p < 0.05$).[11]

- In 48 adult patients with moderate to severe heart failure receiving conventional therapy (ACE inhibitors and diuretics), concomitant treatment with a 15-minute intravenous infusion of sitaxentan 1.5, 3 or 6 mg/kg resulted in selective pulmonary vasodilation, reflecting the reduction in plasma ET-1 levels (plasma ET-1 levels reduced by 21% over 6 hours from a mean baseline value of 15.4 pg/mL).[12] In this double-blind, multicentre trial, during the 6-hour assessment period, there was a significant reduction in pulmonary artery systolic pressure ($p \leq 0.001$), PVR ($p = 0.003$), MPAP ($p = 0.02$) and right atrial pressure ($p = 0.03$) in sitaxentan compared with placebo recipients. However, there was no between-group difference in terms of heart rate, mean arterial pressure (MAP), pulmonary capillary wedge pressure, cardiac index or systemic vascular resistance.
- In another study[13] in patients with heart failure (mean left ventricular ejection fraction [LVEF] of 24%), a 3-minute intravenous infusion of sitaxentan (0.3125–10 mg/min) caused an infusion rate-dependent decrease in local PVR compared with baseline values and with those in patients with a normal LVEF (both $p < 0.05$). By contrast, a sitaxentan infusion did not affect PVR in those with normal LVEF. There were no significant changes from baseline in heart rate, MAP, cardiac index or MPAP.
- Sitaxentan was teratogenic in animal studies; currently, there are no data available in humans.[8]

2. Pharmacokinetic Profile

The pharmacokinetic profile of oral sitaxentan has been investigated in several clinical studies involving a total of 522 patients with PAH, which are reported in the EMEA summary of product characteristics[8] and scientific discussion[10] documents.

- In PAH patients and healthy adult volunteers, sitaxentan exhibits nonlinear pharmacokinetics after oral administration, with the area under the plasma-concentration time curve (AUC) and peak plasma concentrations (C_{max}) increasing in a more than dose-proportional manner with increasing doses.[10]
- Oral sitaxentan (25–100mg) is rapidly absorbed in patients with PAH, with mean C_{max} values generally occurring within 0.5–4 hours.[8] At steady state, after multiple doses of sitaxentan 100mg, the mean values for C_{max}, trough plasma concentration and AUC from time 0 to 24 hours were 13 μg/mL, 0.06 μg/mL and 40 μg • h/mL, respectively.[10] These steady-state values were achieved after 5 days. At the recommended dosage, there is no unexpected accumulation of sitaxentan.[8] The absolute bioavailability of sitaxentan is 70–100%.[8]
- Although the rate of absorption (43% reduction in C_{max} and a 2-fold increase in the time to achieve C_{max}) was reduced in the fasted versus the fed state, the extent of absorption was unchanged (see section 5).[8]
- Sitaxentan shows extensive dose-dependent binding to plasma protein (>99%), predominantly to albumin.[8] The drug does not appear to cross the blood-brain barrier, nor does it penetrate erythrocytes. Sitaxentan was excreted in the breast milk of rats, although it is unknown whether this is the case in humans.
- Sitaxentan is extensively metabolised in healthy volunteers, with *in vitro* studies indicating that this is mediated by cytochrome P450 (CYP) 2C9 and CYP3A4 isoenzymes.[8] The most common metabolites of sitaxentan have no clinically relevant activity (see section 1).
- After a radiolabelled dose of sitaxentan, ≈50–60% of the dose is eliminated via the urine, with the remainder excreted in the faeces.[8] Less than 1% of sitaxentan is eliminated as unchanged drug. The terminal elimination half-life of the drug is 10 hours.
- Sitaxentan inhibits CYP2C9 and, to a lesser extent, CYP2C8, CYP2C19 and CYP3A4/5 in *in vitro* studies using human liver microsomes or primary hepatocytes.[8,10] Thus, plasma concentrations of drugs that are primarily metabolised by these isoenzymes, particularly CYP2C9, may potentially increase when they are coadministered with sitax-

entan. Concomitant administration of sitaxentan with inhibitors of CYP2C9 and CYP2C19 is not predicted to result in clinically relevant drug interactions.

- Concomitant treatment with sitaxentan had no clinically relevant effects on the pharmacokinetics of the CYP3A4/5 substrates nifedipine, sildenafil,[14] ketoconazole (also a CYP2C19 substrate) or nelfinavir (also a CYP2C19 substrate), nor did it have any clinically relevant effect on the pharmacokinetics of omeprazole (CYP2C19 substrate) or digoxin (P-glycoprotein substrate).[8] Vice versa, coadministration of nifedipine or sildenafil with sitaxentan had no clinically relevant effects on the pharmacokinetics of sitaxentan.
- There was a clinically significant 6-fold increase in the plasma concentration of sitaxentan (100mg dose) when the drug was coadministered with ciclosporin (cyclosporine; 3.5 mg/kg twice daily), which is an organic anion transporter protein (OATP) substrate. [8] Concomitant administration of these two agents is contraindicated.
- Exposure to warfarin, a substrate for CYP2C9, was increased 2.4 fold when the drug was coadministered with sitaxentan.[8] Patients receiving concomitant sitaxentan and warfarin require lower doses of warfarin to achieve target International Normalised Ratio (INR), which should be monitored regularly in these patients. Sitaxentan is predicted to cause similar increases in the plasma concentration of other vitamin K antagonists when it is coadministered with these agents.
- There are no clinically relevant effects of gender, race, age or renal impairment on the pharmacokinetic properties of sitaxentan.[8] To date, no pharmacokinetic studies have been conducted in patients with hepatic impairment, but as the drug shows nonlinear pharmacokinetics, hepatic impairment may potentially result in higher plasma concentrations of the drug in this patient population; the drug is contraindicated in this patient population.[8,10]

3. Therapeutic Efficacy

The short-term efficacy of oral sitaxentan for the treatment of adult patients with PAH has been evaluated in three pivotal, large, randomised, double-blind, placebo-controlled, multicentre, multinational trials; namely, the 12-week STRIDE (Sitaxentan To Relieve ImpaireD Exercise)-1 trial[15-18] (n = 178) conducted in North America; the 18-week STRIDE-2[19] trial (n = 245) conducted in the US and Europe; and the 18-week STRIDE-4 trial[20] (n = 98) conducted in Latin America and Spain (available as an abstract). The STRIDE-1 and -2 trials are published in full, although some supplemental data[17,18] are currently available only as abstracts plus posters. These pivotal trials were initiated following results from a small (n = 20), randomised, open-label, fully published, pilot study,[21] which is not discussed further. They are supported by another similarly designed trial, the fully published, 12-week STRIDE-6 trial[22] (data available are for a subgroup analysis of 35 patients experiencing a lack of efficacy with bosentan treatment), and by a noncomparative study (available as abstracts plus posters)[23,24] in 15 patients refractory to or intolerant of bosentan treatment.

The longer-term efficacy (≤2 years' treatment) of sitaxentan has been evaluated in extension studies of the STRIDE-1 (single-centre data from Canada[25-27]) and -2 (i.e. STRIDE-2X[28]) trials. STRIDE-1X data are published in full[25] or available as abstracts[26,27] plus poster[27] or oral[26] presentations, whereas STRIDE-2X data are only available as an abstract.[28]

Patients had moderate to severe (i.e. National New York Heart Association [NYHA]/WHO functional class II–IV) PAH associated with idiopathic PAH, connective tissue disease (CTD) or congenital heart disease.[15,19,20,22] In STRIDE-1 and -2, the majority of patients had NYHA/WHO functional class III disease (66%[15] and 59%[19] of patients), with virtually all other patients having functional class II disease (33%[15] and 37%[19]). Of note, in STRIDE-4,[20] 61% of patients were functional class II and 38% were functional class III; the high proportion of patients in functional class II (i.e. with

less severe disease) differs from the traditional inclusion criteria for previous clinical trials in PAH patients, which limit enrolment to those with functional class III and IV disease.[16] In STRIDE-6,[22] 60% of PAH patients were classified NYHA/WHO functional class III and 26% as functional class II. Exclusion criteria in STRIDE trials included the use of pharmacotherapy for PAH within 14[22] or 30[15,19] days of study entry and having parenchymal lung disease or chronic liver disease.[15,19,20,22]

In STRIDE-1, patients received sitaxentan 100mg or 300mg or placebo once daily for 12 weeks;[15] those in STRIDE-2 received sitaxentan 50mg or 100mg or placebo once daily for 18 weeks or open-label treatment with the recommended dosage of bosentan (i.e. 62.5mg for 4 weeks twice daily, then 125mg twice daily for the remainder of the study);[19] those in STRIDE-4 received sitaxentan 50mg or 100mg or placebo once daily for 18 weeks;[20] and those in STRIDE-6 received sitaxentan 50 or 100mg once daily.[22] With the exception of bosentan, all treatment was given in a double-blind manner in the STRIDE trials. In other studies,[23,24] patients refractory to or intolerant of bosentan were switched to sitaxentan 100mg once daily for up to 6 months. In addition to sitaxentan, all patients were receiving current conventional therapies, which could include a combination of digoxin, anticoagulants, diuretics, oxygen and/or vasodilators (e.g. calcium channel blockers, ACE inhibitors). Discussion in this section focuses on patients receiving the recommended dosage of sitaxentan 100mg once daily (see section 5).

The primary endpoint in STRIDE-1[15] was the change in the percentage of predicted peak oxygen consumption (VO_2) at 12 weeks and that in STRIDE-2[19] and STRIDE-4[20] was the change from baseline in the distance walked in 6 minutes (6MWD) at 18 weeks. Secondary or other endpoints in clinical trials included the change from baseline in 6MWD,[15,22-24] shifts from baseline in NYHA/WHO functional class,[15,19,22] cardiopulmonary haemodynamic changes from baseline[15] and the time to clinical worsening (TCW).[15,19,20] TCW was defined as the time between the first dose of study drug and the date at which the first of the following events occurred (events specified differed between STRIDE-1 and -2, and were not defined in the abstract presentation for STRIDE-4): death,[15,19] transplantation,[15,19] atrial septostomy,[15,19] epoprostenol use,[15] initiation of additional chronic treatment for the disease (i.e. therapy escalation),[19] hospitalisation for PAH[19] or combined WHO functional class deterioration and ≥15% decrease in 6MWD.[19] Where reported, statistical analyses were based on the modified intent-to-treat population (i.e. patients who had received at least one dose of study drug).[15,19] STRIDE-2 was not designed to evaluate the relative efficacy of sitaxentan versus bosentan, with the latter open-label arm included for observational purposes only.[19]

Pivotal Phase III Trials

- In STRIDE-1, after 12 weeks' treatment, there was no difference in the mean change from baseline in the percentage of predicted peak VO_2 between the sitaxentan 100mg (n = 55) and placebo (n = 60) groups (mean reduction 0.4% vs 0.1% from baseline values of 45% and 48%), although those receiving sitaxentan 300mg (n = 63) experienced a significant improvement relative to the placebo group (3% increase from baseline value of 45% vs 0.1% reduction; p = 0.005) [primary endpoint].[15] However, as stated by the EMEA,[8] the clinical relevance of this endpoint is uncertain.
- At the recommended dosage (i.e. 100mg once daily), the improvement in mean 6MWD from pretreatment values to study end was significantly greater with sitaxentan than with placebo treatment in the STRIDE-1[15] and STRIDE-2[19] trials (figure 1) [primary endpoint for STRIDE-2]. The placebo-corrected increase in the sitaxentan 100mg groups was 35 metres ($p < 0.01$) after 12 weeks' treatment in STRIDE-1[15] and 31.4 metres (p = 0.03) after 18 weeks' treatment in STRIDE-2.[19]
- However, in STRIDE-4, there was no significant difference between the sitaxentan 100mg and placebo groups in terms of changes in 6MWD after 18 weeks' treatment (figure 1) [primary endpoint].[20] The improvement in exercise capacity was signifi-

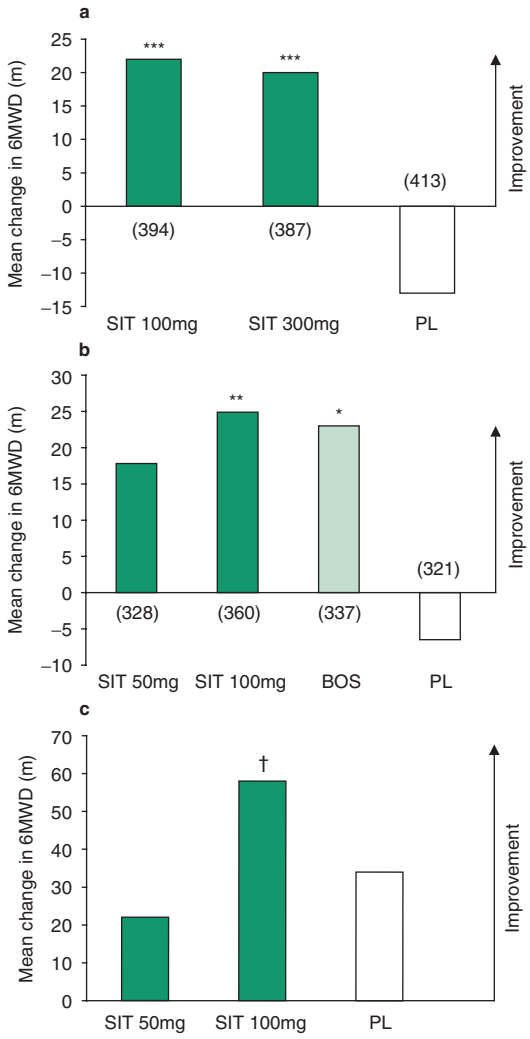


Fig. 1. Efficacy of oral sitaxentan (SIT) in patients with moderate to severe pulmonary arterial hypertension (PAH). Mean change from baseline in the distance walked in 6 minutes (6MWD) after 12[15] or 18[19,20] weeks (i.e. at study end) in pivotal, randomised, double-blind, multicentre, multinational trials: **(a)** STRIDE-1 trial[15] (secondary endpoint), **(b)** STRIDE-2 trial[19] (primary endpoint) and **(c)** STRIDE-4 trial[20] (primary endpoint; abstract presentation). Where reported, baseline 6MWD values appear in brackets. In STRIDE-1,[15] patients received SIT 100mg (n = 55) or 300mg (n = 63) or placebo (PL; n = 60) once daily; participants in STRIDE-2[19] received SIT 50mg (n = 62) or 100mg (n = 61) or PL (n = 62) once daily or open-label treatment with the recommended dosage of bosentan (BOS; n = 60); and those in STRIDE-4 received SIT 50 or 100mg (n = 32 per group) or PL (n = 34) once daily. * p = 0.05, ** p = 0.03, *** p < 0.01 vs PL; † p = 0.014 vs SIT 50mg.

cantly greater in the sitaxentan 100mg than in the 50mg group (58 vs 22m; p = 0.014).

- Of note, the majority (61%) of patients enrolled in STRIDE-4 had WHO functional class II disease making the study underpowered to detect a between-group difference versus placebo treatment (i.e. primary endpoint).[20] In a *post hoc* subgroup analysis of patients with functional class III and IV disease in the sitaxentan 100mg group, the treatment effect for the difference in 6MWD versus the placebo group significantly favoured the sitaxentan group (difference of 56m; p < 0.04). Similarly, in a retrospective analysis of a subgroup of patients with functional class III or IV disease participating in STRIDE-1, sitaxentan-treated patients (n = 47; pooled data from 100mg and 300mg group) experienced a beneficial improvement in 6MWD, whereas placebo recipients (n = 23) had a deterioration in their exercise capacity (+39 vs −26m; p < 0.001).[16]

- Sitaxentan treatment significantly improved most cardiopulmonary haemodynamic variables compared with placebo after 12 weeks' treatment in STRIDE-1.[15] For example, in the sitaxentan 100mg group, the mean right atrial pressure did not change from baseline (7mm Hg), whereas it increased by 1mm Hg in the placebo group (p < 0.005; baseline 8mm Hg); the cardiac index increased by 0.3 L/min/m^2 versus no change from baseline in the placebo group (p < 0.02; baseline 2.4 L/min/m^2 both groups); and PVR was reduced by 221 dyn/s/cm^{-5} in the sitaxentan group but increased in the placebo group by 49 dyn/s/cm^{-5} (p < 0.001) [baseline values 1026 and 911 dyn/s/cm^{-5}]. There was no significant between-group difference in MPAP over this time period.

- Very few sitaxentan-treated patients experienced clinical worsening of their disease. In STRIDE-1, no patients in the sitaxentan 100mg group experienced clinical worsening (as defined previously) of their disease versus three (5% of 60 patients) patients in the placebo group.[15] In STRIDE-2, four sitaxentan 100mg and ten placebo recipients experienced at least one clinical worsening event; the first clinical worsening events to occur were hospitalisation for PAH (1 vs 4 placebo recipients), initiation of new

chronic PAH treatment (3 vs 4 patients) and combined WHO functional class deterioration and ≥15% decrease in 6MWD (0 vs 2 patients).[19]

- In the STRIDE-1[15] and -2[19] trials, there was no significant difference between the sitaxentan 100mg and placebo groups in terms of the TCW. However, in a pooled analysis[29] of these two trials that used the more stringent definition of TCW as defined in STRIDE-2, the estimated TCW was significantly ($p = 0.046$) prolonged in those receiving sitaxentan 100mg (n = 115) compared with placebo recipients (n = 119), based on a Kaplan-Meier plot [abstract presentation].
- By study end, improvements in NYHA/WHO functional class were significantly better in sitaxentan 100mg than in placebo groups of the STRIDE-1,[15] -2[19] and -4[20] trials (no quantitative data reported for STRIDE-4). For example, in STRIDE-1,[15] after 12 weeks' treatment 29% of patients in the sitaxentan 100mg group experienced an improvement in NYHA functional class versus 15% of those in the placebo group ($p < 0.02$); NYHA functional class worsened in 0% and 7% of recipients, respectively.

In Subgroups of Patients

- In an intent-to-treat subgroup analysis of participants in STRIDE-1 with PAH associated with CTD, sitaxentan treatment (100 or 300mg once daily; n = 33) improved 6MWD (+20 vs −38m; $p < 0.027$; baseline values of 340 and 414m), NYHA functional class and cardiopulmonary haemodynamic parameters relative to placebo (n = 9).[17,18] Twenty-four percent (8 of 33 patients) of sitaxentan-treated patients improved by one NYHA functional class, with no patients showing a deterioration of functional class, whereas 11% of those in the placebo group improved by one functional class and a further 11% had a deterioration of one functional class. At baseline, all patients were classified as NYHA functional class II (approximately one-third of patients) or III.
- In a pooled analysis of STRIDE -2 and -4 participants with PAH associated with congenital heart disease, sitaxentan 100mg once daily (n = 9) significantly (both $p < 0.05$) improved exercise capacity compared with placebo (n = 16) at 12 (between-group difference for 6MWD of 42m) and 18 weeks (between-group difference of 64m) [abstract presentation].[30] Respective baseline values were 349 and 312 metres.
- In 15 patients enrolled in STRIDE-6 who had failed to respond to previous bosentan treatment, switching to sitaxentan 100mg once daily for 12 weeks improved exercise capacity (i.e. an increase in 6MWD of >15%) and Borg dyspnoea score (i.e. >1 unit decrease in score) in 33% and 27% of patients.[22] Most of the remaining patients showed no change in 6MWD (47% of patients) and Borg dyspnoea score (53%).
- In addition, 7% of these 15 patients improved by one WHO functional class, 80% had no change in functional class and 13% had a deterioration of one functional class.[22] Four recipients of sitaxentan 100mg experienced clinical worsening of PAH, generally during the first 5 weeks' treatment (75% of patients). Clinical worsening included hospitalisation for worsening of PAH in one patient and, in the remaining three patients, initiation of a new long-term treatment of PAH because of a combined decrease in functional class and a >15% decrease in 6MWD.
- These data in bosentan-refractory patients were supported by an open-label study in 15 PAH patients, 12 of whom were refractory to bosentan treatment and 3 of whom had bosentan-related liver abnormalities (liver function was normalised before initiating sitaxentan therapy).[23,24] After 6 months' treatment with sitaxentan 100mg once daily, all patients experienced an increase of >10% in 6MWD and one patient had improved by one WHO functional class. Also see section 4 for discussion of tolerability results from this study.
- Sitaxentan treatment significantly improved quality of life (QOL), particularly in domains related to physical ability, in patients with idiopathic PAH (n = 19) or PAH caused by CTD (n = 4).[31] After 16 weeks, there were significant (all $p < 0.05$) improvements from baseline scores in the domains of physical functioning (37 at baseline vs 48), role physical (39.5 vs 58), general health (48 vs 61),

vitality (46 vs 60) and social functioning (61 vs 75), as assessed the Short-Form 36 QOL questionnaire (all values estimated from a graph).

Longer-Term Extension Studies

- After up to 2 years' treatment in a compassionate use extension study of STRIDE-1, 9 of 11 PAH patients continued to benefit from open-label sitaxentan therapy; one patient deteriorated at 7 months and subsequently died from progressive PAH and one patient withdrew at ≈18 months with myeloma.[25-27] After 1 year (n = 10), exercise capacity significantly improved from baseline (mean 6MWD 436 vs 386m at baseline; p = 0.04),[25] with these benefits sustained at 2 years (n = 9; mean 6MWD 440 vs 386m; p = 0.02).[26,27]
- Additionally, sitaxentan treatment improved the WHO functional class status of these patients. After 1 year, all ten patients were classified as WHO functional class II versus one patient at baseline ($p < 0.01$); the other nine patients were functional class III at baseline.[25] The nine patients who continued sitaxentan therapy throughout the subsequent year remained in WHO functional class II at 2 years.[26,27]
- After 1 year, cardiopulmonary haemodynamic parameters showed no change (MPAP and mean pulmonary artery wedge pressure) or improved significantly from baseline (mean cardiac output 5.4 vs 4.3 L/min at baseline and mean PVR 585 vs 742 dyn/s/cm^{-5}; p = 0.009 and p = 0.04, respectively) in this extension study.[25]
- According to interim data from the open-label STRIDE-2X extension study, sitaxentan-treated patients (n = 125) had a significantly lower 1-year risk of discontinuing monotherapy than those receiving bosentan (n = 84) [25% vs 42%; p = 0.003].[28] There was no significant between-group difference in the median change in 6MWD at 12 months or in the estimated time to WHO functional class improvement, although the study was not designed to evaluate these endpoints.

4. Tolerability

Short- and longer-term (≤2 years) treatment with oral sitaxentan was generally well tolerated in adult patients with moderate to severe PAH participating in clinical trials discussed in section 3. Discussion in this section focuses on a pooled analysis of patients receiving sitaxentan 100mg once daily in placebo-controlled clinical trials, as reported in the EMEA summary of product characteristics,[8] and data reviewed by Barst.[32]

- The most common adverse events that were considered to be at least possibly related to sitaxentan treatment in placebo-controlled trials were headache (15%), peripheral oedema (9%) and nasal congestion (9%).[8] Adverse events that were considered at least possibly related to sitaxentan treatment and to occur with ≥2% higher incidence in the sitaxentan than in the placebo group were peripheral oedema, insomnia, nasal congestion, epistaxis, nausea, constipation, flushing, an increased INR and a prolonged prothrombin time.
- As a class, ET receptor antagonists have been associated with the development of liver function abnormalities.[32] A pooled analysis of the pivotal phase III clinical trials discussed in section 3 showed that elevations in ALT and/or AST of >3× the upper limit of normal (ULN) occurred in 2% of patients receiving sitaxentan 100mg once daily (n = 147) and 5% of placebo recipients (n = 153).[32]
- Generally, liver function abnormalities progressed slowly, were asymptomatic and were reversible upon discontinuation of treatment.[8,32] One patient died from hepatic failure during treatment with sitaxentan (initially 600 mg/day).[8,10]
- After 1 year of treatment, no serious adverse events had occurred and there were no occurrences of liver function abnormalities in ten patients participating in the compassionate use extension of STRIDE-1.[25]
- In STRIDE-2X, there was a significantly (p = 0.01) lower 1-year risk of sitaxentan (n = 145) than bosentan (n = 84) recipients developing liver function abnormalities (4% vs 14%), as assessed using Kaplan-Meier analysis.[33] There was also a reduction in the 1-year risk of discontinuing treatment due

to liver function abnormalities in the sitaxentan group (1% vs 9%; $p < 0.01$).

- The majority (87%; 27 of 31 recipients) of PAH patients who had developed liver function (i.e. ALT or AST >3× ULN) abnormalities during prior bosentan treatment had no recurrence of liver function abnormalities during subsequent treatment with sitaxentan 50 or 100mg once daily [abstract plus poster presentation].[34] This was a pooled analysis of patients participating in the STRIDE-3 and -6 trials; sitaxentan treatment was not initiated until after liver function was normalised. Three of the four sitaxentan-treated patients who had a recurrence of liver function abnormalities (occurring at weeks 8, 12, 13 and 13) discontinued treatment.
- These data are supported by a study discussed in section 3 in patients initiating sitaxentan treatment after experiencing bosentan-related liver function abnormalities.[23,24] In these two studies, one patient[24] experienced a transient liver function abnormality after initiating sitaxentan treatment but this did not necessitate discontinuation of treatment.
- In a pooled analysis of placebo-controlled trials, the overall mean decrease in haemoglobin levels in sitaxentan-treated patients was 0.5 g/dL, with 60% of 149 sitaxentan and 32% of 155 placebo recipients experiencing a reduction in haemoglobin level of ≥1 g/dL.[8] A decrease of >15% from baseline and that was less than the lower limit of normal occurred in 7% of sitaxentan versus 3% of placebo recipients.

5. Dosage and Administration

In Europe,[8] oral sitaxentan is recommended for the treatment of adult patients with PAH classified as WHO functional class III to improve exercise capacity. Efficacy has been shown in idiopathic PAH and in PAH associated with CTD. The recommended dosage is 100mg once daily, with the drug taken without regard to food (see section 2) and no dose titration required. Local prescribing information should be consulted for additional information on precautions, drug interactions and contraindications associated with sitaxentan treatment.

6. Sitaxentan: Current Status in Pulmonary Arterial Hypertension

Oral sitaxentan is a highly selective ET_A receptor antagonist, with a favourable pharmacokinetic profile that permits convenient once-daily administration. The drug is approved in Europe for use in patients with PAH classified as WHO functional class III. In two pivotal placebo-controlled trials in patients with moderate to severe PAH (majority classified as NYHA/WHO functional class III), 12–18 weeks' treatment with sitaxentan 100mg once daily significantly improved 6MWD and NYHA/WHO functional class and was generally well tolerated. These data are supported by a subgroup analysis of PAH patients classified as functional class III and IV who participated in the third pivotal placebo-controlled trial. The beneficial effects of sitaxentan treatment were maintained in extension studies of up to 2 years' duration.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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