



# Inhibition of endothelin receptors in the treatment of pulmonary arterial hypertension: does selectivity matter?

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Treatment options for pulmonary arterial hypertension (PAH) have considerably improved in the past few years. Endothelin (ET)-receptor antagonism has been established as a first-line option for the majority of PAH patients. Endothelin-receptor antagonists (ETRAs) comprise sulfonamide and non-sulfonamide agents with different affinities for ET-receptor subtypes (ET<sub>A</sub> and ET<sub>B</sub>), and the focus of development has shifted from drugs with less selectivity to those with high selectivity. There is ongoing debate as to whether selective or non-selective ET-receptor antagonism is more beneficial in the treatment of PAH. This paper reviews the current evidence from experimental and clinical studies obtained from a thorough literature search focusing on the three marketed drugs bosentan, sitaxentan, and ambrisentan. A clinically meaningful difference among the three approved ETRAs with respect to their ET-receptor selectivity could not be demonstrated to date. Therefore, in clinical practice, other features are likely to be of greater relevance when considering treatment, such as the potential for serious drug–drug interactions, convenience of dosing schedule, or rates of limiting side effects. These characteristics bear more relation to the chemical or pharmacological properties of the drugs than to receptor selectivity itself.

## Keywords

Endothelin • Receptor selectivity • Pulmonary arterial hypertension • ET<sub>A</sub>/ET<sub>B</sub> • ETRA • ET-1 • Bosentan • Sitaxentan • Ambrisentan

## Introduction

Pulmonary arterial hypertension (PAH) is a group of diseases characterized by progressive increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP), resulting in right ventricular failure and premature death.<sup>1,2</sup> A number of drug classes have been approved for this indication on the basis of randomized, controlled trials, namely prostanoids (epoprostenol, iloprost, and treprostinil), phosphodiesterase-5-inhibitor (sildenafil), and endothelin (ET)-receptor antagonists (ETRAs) (bosentan, sitaxentan, and ambrisentan).<sup>3</sup> The ETRA drug class comprises sulfonamide and non-sulfonamide agents with different affinities for endothelin-receptor (ET) subtypes, and there are continuing discussions as to whether selective or non-selective ET-receptor antagonism is more beneficial in the treatment of PAH. This paper reviews the current evidence from experimental

and clinical studies obtained from a thorough literature search using the general search terms 'endothelin receptor antagonist' and 'pulmonary (arterial) hypertension'. Particular focus has been placed on clinical articles.

## Effects of endothelin-1 mediated via ET<sub>A</sub> and ET<sub>B</sub> receptors

The human endothelin (ET) family consists of three 21-amino acid isopeptides: ET-1, ET-2, and ET-3. Of these, only ET-1 plays an important physiological and pathophysiological role, especially in the regulation of vascular tone. ET-1 is released principally from endothelial cells that line blood vessels, but also from other vascular and non-vascular cells. Most of its effects are paracrine, the most striking of which is its extremely potent and long-lasting

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vasoconstrictor action.<sup>4</sup> In addition, ET-1 is profibrotic and involved in the pathogenesis of various diseases, including PAH. Specifically, ET-1 can induce hypertrophy and hyperplasia in various cell types,<sup>5</sup> fibroblast proliferation,<sup>6</sup> extracellular matrix production,<sup>7</sup> inflammation,<sup>8</sup> and neuro-humoral stimulation.<sup>9</sup> Furthermore, it stimulates the generation of other local mediators of vascular tone, including nitric oxide (NO), prostacyclins, and platelet-activating factors.<sup>10</sup> These factors modulate the effects of ET-1 in the cardiovascular system through their vasorelaxant action and anti-proliferative potential.

Circulating plasma ET-1 levels are elevated in atherosclerosis, arterial hypertension, heart failure, and PAH<sup>11</sup> when compared with the normal state. Of note, ET-1 plasma levels correlate with parameters of pulmonary haemodynamics,<sup>12</sup> and predict survival in patients with untreated PAH.<sup>13</sup>

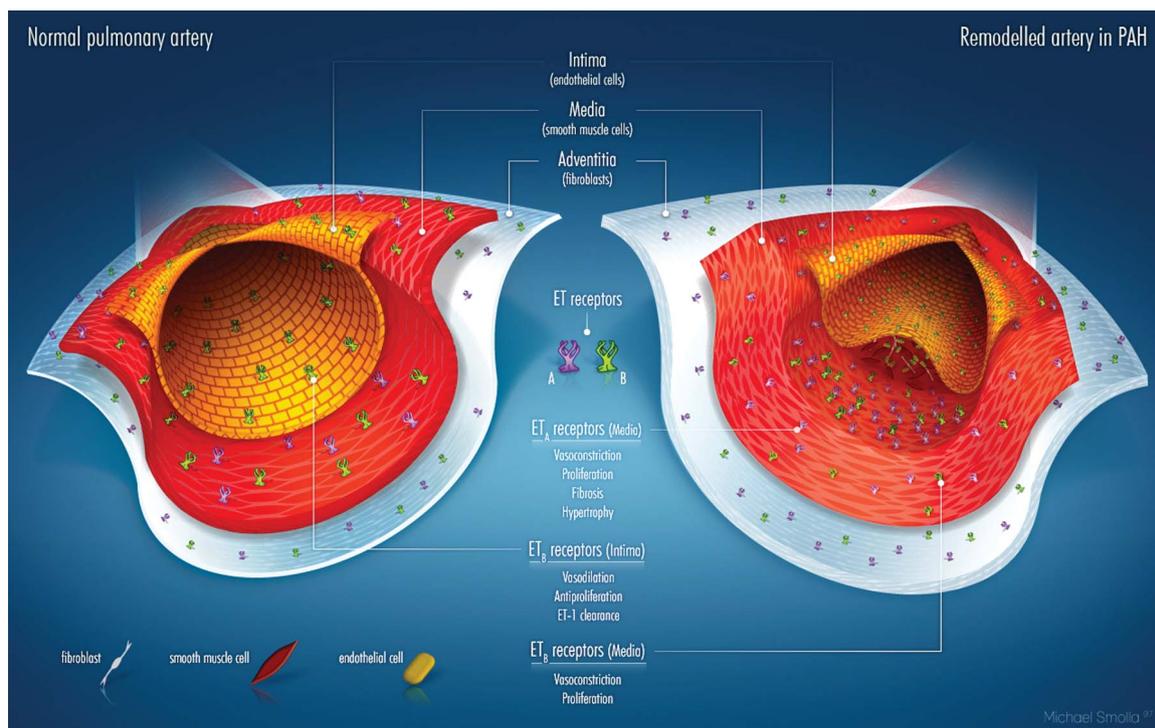
### ET<sub>A</sub>- vs. ET<sub>B</sub>-mediated effects

Within the mammalian cardiovascular system, ET-1 acts through two receptor subtypes—ET<sub>A</sub> and ET<sub>B</sub>. In the vasculature, ET<sub>A</sub> receptors are located on smooth muscle cells (SMCs) and fibroblasts, whereas ET<sub>B</sub> receptors are predominantly localized on endothelial cells and, to a lesser extent, on SMCs, fibroblasts, and macrophages. Recent data using cultured transfected cell lines suggest that ET<sub>A</sub> and ET<sub>B</sub> receptors can form constitutive heterodimers (dimerization theory). Functionally, this means that ET<sub>B</sub>

receptors expressed on SMCs couple with ET<sub>A</sub> receptors, and the former adopt the function of the latter, such that ET<sub>B</sub> receptors in heterodimers mediate vasoconstriction similar to ET<sub>A</sub> receptors.<sup>14</sup> Furthermore, it has been suggested that selective antagonism of one ET-receptor subtype only may result in compensation by the other receptor. This experimental hypothesis has been called ‘cross-talk’.<sup>15,16</sup>

Under normal physiological conditions, the receptor types have broadly opposing functions (Figure 1). Activation of ET<sub>A</sub> receptors mediates vasoconstriction,<sup>4</sup> proliferation,<sup>17,18</sup> hypertrophy,<sup>5,19</sup> cell migration,<sup>20</sup> and fibrosis, whereas activation of endothelial ET<sub>B</sub> receptors stimulates the release of potent vasodilators (NO and prostacyclin), which exhibit anti-proliferative properties, and prevents apoptosis.<sup>21</sup> Importantly, ET<sub>B</sub> receptors on endothelial cells mediate the clearance of circulating ET-1 in the lungs, kidney, and liver, with up to 50% of mature ET-1 in healthy subjects and 40% in patients with PAH cleared via pulmonary ET<sub>B</sub> receptors.<sup>22</sup> Endothelial cell ET<sub>B</sub>-receptor activation also inhibits ET converting enzyme-1, the enzyme that is required to produce mature ET-1.<sup>23</sup>

Alterations in the distribution and number of ET<sub>A</sub> and ET<sub>B</sub> receptors in conditions such as PAH suggest that their roles in the disease state may differ from those in normal physiology. For example, there are more ET-1-binding sites in the distal pulmonary vessels of patients with PAH, and ET<sub>B</sub> receptors are also



**Figure 1** Schematic of the distribution of ET<sub>A</sub> and ET<sub>B</sub> receptors in various layers of the vessel wall of a small pulmonary artery in the healthy state (left) and in PAH (right). In the intima, only ET<sub>B</sub> receptors are expressed, in the media both ET<sub>A</sub> and ET<sub>B</sub>, and in the adventitia only ET<sub>A</sub>. In the diseased artery, structural changes (intima structure not intact with schematic illustration of plaque; media with smooth muscle cell proliferation, adventitia thickened) are evident. In terms of functional changes, the number/density of ET receptors of both types increases in all vessel layers, however, the ET<sub>A</sub> receptors to a greater extent.

upregulated.<sup>24</sup> ET<sub>B</sub> receptors may not exclusively mediate pulmonary vasodilatation. Because of the effects of a sub-population of ET<sub>B</sub> receptors located on SMC and fibroblasts, the spectrum of possible adverse effects of ET<sub>B</sub>-receptor stimulation in patients with pulmonary hypertension includes the induction of vasoconstriction,<sup>15,25</sup> proliferation,<sup>24,26</sup> and fibrosis.<sup>27</sup>

Early suggestions that the endothelium might be dysfunctional, resulting in diminished expression or loss of function of the ET<sub>B</sub> receptors,<sup>28</sup> have recently been challenged by the findings of Langleben *et al.*,<sup>29</sup> who observed intact or only modestly reduced ET<sub>B</sub>-mediated clearance of ET-1 in patients with pulmonary hypertension of various aetiologies. The authors concluded that the ET-1 levels are increased primarily because of excess synthesis rather than reduced clearance of ET-1.

## Receptor selectivity and endothelin plasma levels

Endothelin-receptor antagonists are usually categorized according to their selectivity for ET<sub>A</sub> or ET<sub>B</sub> receptors. The ET<sub>A</sub> pharmacological probe, BQ-123, is considered the benchmark for a selective ETRA, based on an ET<sub>A</sub>:ET<sub>B</sub> binding ratio of 2000:1 in a standard *in vitro* assay.<sup>30,31</sup> To some extent, however, the definition of receptor selectivity is arbitrary, given the wide variation in values obtained using different experimental systems. For example, the ETRA ambrisentan has been reported to have an ET<sub>A</sub>:ET<sub>B</sub> selectivity ranging from 29:1 for ET-1-mediated contraction in the rat aorta<sup>32</sup> to 4000:1 in myocardial membranes.<sup>33</sup>

An indication of functional selectivity can be gained from observations of the effects of different ETAs on circulating ET-1 levels *in vivo*. For example, sitaxentan (*in vitro* ET<sub>A</sub>:ET<sub>B</sub> selectivity >6500:1) acutely decreases ET-1 levels in patients with chronic heart failure,<sup>34</sup> indicating that ET<sub>B</sub> receptors, which play a role in ET-1 clearance, remain functional. In contrast, bosentan and less-selective ET<sub>A</sub>-receptor antagonists (ET<sub>A</sub>:ET<sub>B</sub> ratio <2000:1) increase plasma ET-1 in healthy volunteers and in patients with

heart failure or PAH (Table 1). Interestingly, significant increases of ET-1 levels occurring 2 h following ingestion have been reported with ambrisentan (widely reported to be selective for ET<sub>A</sub>), suggesting that its functional selectivity may differ from that observed *in vitro*.<sup>35</sup> Whether elevated ET-1 levels seen in ETRA-treated PAH patients have pathophysiological or prognostic significance remains unknown.

## Experimental evidence

### Endothelin-receptor selectivity and its vasoconstriction and vasodilation effects

Vasodilation is an important goal of therapeutic intervention for PAH. Theoretically, selective ET<sub>A</sub>-receptor antagonists should be more effective in achieving this than non-selective ET<sub>A</sub>-/ET<sub>B</sub>-receptor antagonists, given the role played by ET<sub>B</sub> receptors in both vasodilation and ET-1 clearance. In animal models of PAH, however, positive dilatory effects have been observed with both selective ET<sub>A</sub>-receptor blockade and non-selective antagonism<sup>36</sup> (see Supplementary material online).

Since direct evaluation of the pulmonary circulation requires invasive procedures, the majority of the available data are extrapolated from human studies performed on blood vessels in the systemic circulation.<sup>37,38</sup> Collectively, these studies indicate that: (i) selective ET<sub>A</sub>-receptor blockade results in a robust vasodilator response and increased blood flow; (ii) selective ET<sub>B</sub>-receptor blockade results in vasoconstriction and reduced blood flow; and (iii) co-administration of selective ET<sub>A</sub>- and ET<sub>B</sub>-receptor antagonists attenuates the vasodilator response relative to selective ET<sub>A</sub>-receptor blockade (see Supplementary material online). However, although these data provide information regarding the effects of receptor selectivity on blood vessel tone in general, they do not provide precise information on how these drugs work in the pulmonary arterial circulation.

**Table 1** Effects of endothelin receptor antagonists on ET-1 plasma levels in humans

Study	Indication	Design	n	Dose	Interval	Effect on ET-1 level
<b>Bosentan</b>						
Kiowski <i>et al.</i> <sup>101</sup>	CHF	r, pc, db	24	100–200 mg i.v. (single ascending dose)	1 h	↑ >2.0×
Sütsch <i>et al.</i> <sup>102</sup>	CHF	r, pc, db	36	1000 mg b.i.d. oral	3 h (Day 1)	↑ >2.0×
				Chronic 1000 mg b.i.d.	3 h (Day 14)	↑ >1.3×
Weber <i>et al.</i> <sup>103</sup>	Healthy volunteers	r, pc, db	8	3–2400 mg oral		↑ 2×
				10–750 mg i.v. (single ascending doses)		↑ 3×
Williamson <i>et al.</i> <sup>105</sup>	PAH	o	7	50, 150, and 300 mg i.v.	6 h	↑ 2× (dose dependent)
Hiramoto <i>et al.</i> <sup>106</sup>	PAH	o	7	62.5 mg (single oral dose)	6 h	↑ 2.0×
<b>Sitaxentan</b>						
Givertz <i>et al.</i> <sup>34</sup>	CHF	o	47	0.5, 3.0, or 6.0 mg/kg	6 h	↓ 0.8×
<b>Ambrisentan</b>						
FDA report <sup>35</sup>	Healthy volunteers	o	7	5 mg (single oral dose)	2 h	↑ 1.6 pg/mL <sup>a</sup>
			7	10 mg (single oral dose)	2 h	↑ 1.1 pg/mL <sup>a</sup>

<sup>a</sup>Placebo-subtracted median. CHF, congestive heart failure; db, double-blind; h, hours; i.v., intravenous; o, open; PAH, pulmonary arterial hypertension; pg, picogram; pc, placebo controlled; r, randomized.

## Endothelin-receptor selectivity and its effects on vascular remodelling

Several studies in animal models document that ETRAs, both non-selective<sup>39,40</sup> and ET<sub>A</sub> selective,<sup>41–43</sup> prevent, attenuate, or even reverse vascular remodelling and/or hypertrophy. For example, in a rat model, during a 2 week hypoxia exposure, sitaxentan<sup>43</sup> and bosentan<sup>39</sup> significantly prevented the increase in PAP, and prevented the pulmonary vascular remodelling. During a 6 week hypoxia exposure, both drugs partially reverted pre-established pulmonary vascular remodelling. Interestingly, sitaxentan,<sup>43</sup> but not bosentan,<sup>39</sup> prevented the increase in ET-1 levels when treatment was initiated early, with hypoxia. In contrast, late treatment, 2 weeks after initiation of hypoxia, did not affect the established elevation of ET-1 level.

## Endothelin-receptor selectivity and fibrosis

Extra-vascular anti-mitotic and anti-fibrotic effects of ETRAs may result in greater efficacy in scleroderma than therapies directed exclusively at the vasculature.<sup>44–46</sup> Data from animal models using either ET<sub>A</sub>-selective or non-selective ETRAs<sup>47–53</sup> demonstrate an amelioration of ET-1-related effects involving the reduction of growth factor expression, extracellular matrix deposition, and matrix metalloproteinase activity.

*In vitro* data with skin fibroblasts suggested that targeting both the ET<sub>A</sub> and the ET<sub>B</sub> receptors is preferable in order to block collagen type I and III production.<sup>54</sup> However, subsequent *in vitro* data using lung fibroblasts indicate that ET-1 induces collagen matrix contraction through the ET<sub>A</sub> receptor, but not the ET<sub>B</sub> receptor.<sup>55</sup> Furthermore, while there is evidence that ET<sub>B</sub> receptors are linked to collagen production *in vitro*, *in vivo* animal data with ET<sub>A</sub> antagonists have shown that they effectively block the accumulation of collagen I, III, and IV,<sup>56</sup> normalize pro-collagen I and III mRNA,<sup>49</sup> and abolish the effect of ET-1 on pro-collagen metabolism.<sup>57</sup> Likewise, although there is evidence that under certain conditions ET-1 can act as a mitogen *in vitro* through both ET<sub>A</sub>- and ET<sub>B</sub>-receptor activation,<sup>58</sup> ET<sub>B</sub> receptors have been shown to inhibit vascular SMC proliferation *in vivo*.<sup>59</sup> It has been suggested that ET<sub>B</sub> receptors may be up-regulated on SMCs and fibroblasts in certain disease states such as scleroderma lung disease.<sup>60</sup> However, the spatial distribution of these receptors among different cell types within the lung microcirculation remains unclear, as does the significance of any increased ET<sub>B</sub>-receptor expression in PAH.

## Clinical trials in pulmonary arterial hypertension patients

ETRA have been studied in numerous open and several controlled clinical trials in patients with PAH. The differences between the

**Table 2** Pharmacological and pharmacokinetic characteristics of approved endothelin-receptor antagonists

Parameter	Bosentan	Sitaxentan	Ambrisentan
Structure	Etherocyclic sulfonamide	Amidothiophene sulfonamide	Diphenyl propionic acid
Selectivity ET <sub>A</sub> :ET <sub>B</sub>	30:1	6500:1	4000:1
ET plasma levels after administration	↑	↓	↑
Approved daily dosing	125–250 mg	100 mg	5–10 mg
Titration	Yes	No	Yes
Resorption			
Absolute bioavailability	~50%	70–100%	High (% not reported)
Food effect on resorption	No	No	No
Time to max. plasma concentration (t <sub>max</sub> ) (h)	3–5	1–4	1.7–3.3
Distribution			
Albumin binding (%)	>98	>99	99
Metabolism and excretion			
Terminal elimination half-life (h)	5.4	10	15
Steady state (days)	3–5	6	3–4
Metabolism	Hepatic (CYP)	Hepatic (CYP)	Hepatic (CYP and glucuronidation; P-gp)
Cytochromes (CYP) p450 mainly involved	CYP 2C9 ↑, 3A4 ↑	CYP 2C9 ↓	CYP 3A4 ↑, 2C19 ↑
Excretion in urine (%)	<3	50–60	Low
Significant drug–drug interactions	Sildenafil, glibenclamide, warfarin, and cyclosporin A	Warfarin and cyclosporin A	Cyclosporin A <sup>a</sup>

EPAR Thelin®<sup>99</sup>, EPAR Tracleer®<sup>98</sup>, Barst®<sup>89</sup>, Vatter and Seifert<sup>107</sup>, and PI Letairis®.

CYP: ↑ drug induces; ↓ drug inhibits; P-gp, P-glycoprotein.

<sup>a</sup>Not for sildenafil or warfarin. Note: drug interaction potential of ambrisentan according to Letairis® prescribing information 'not well characterized'.

three approved drugs may be because of ET-receptor selectivity, but also linked to other properties, such as pharmacokinetics or drug–drug interactions. Table 2 provides an overview of the pharmacological properties of the three available ETAs. Patient characteristics and outcomes of the pivotal studies of each agent are shown in Table 3 and discussed below.

## Bosentan

Bosentan is an orally active, non-peptidic, non-selective, sulphonamide-class  $ET_A/ET_B$  antagonist with twice-daily (b.i.d.) dosing. It was the first ETRA to receive approval for the treatment of patients with PAH in NYHA functional class III (Europe, USA, and Canada) and IV (USA and Canada) at a target dose of 125 mg b.i.d.

In two randomized, controlled trials, bosentan was shown to improve exercise capacity, functional class, haemodynamics, and time to clinical worsening.<sup>61,62</sup> Additional open-label, long-term studies in patients with PAH demonstrated persistent efficacy of bosentan over time and potential for improved survival, compared with predicted survival.<sup>63,64</sup>

Since these first pivotal studies, significant benefits of bosentan treatment have been shown in separate studies ('Bosentan Randomized Trials of Endothelin Antagonist Therapy': BREATHE) in children with PAH<sup>65</sup> [BREATHE-3: idiopathic PAH and congenital heart disease (CHD)], in PAH associated with HIV<sup>66</sup> (BREATHE-4), in patients with PAH and Eisenmenger syndrome<sup>67</sup> (BREATHE-5), and in patients with portopulmonary hypertension.<sup>68</sup>

In addition, the 'Endothelin Antagonist tRIal in miLdLY symptomatic PAH patients' (EARLY) was the first study specifically designed to evaluate the effects of ETRA treatment in 185 PAH patients in functional class II. Preliminary results from this 6 month trial highlight a significant reduction in PVR while the other primary endpoint, the 6 min walk distance (6MWD), did not reach statistical significance. The secondary endpoint, time to clinical worsening, showed a significant improvement with bosentan, translating into a 70% risk reduction.<sup>69</sup>

In another group of 157 patients with chronic thrombo-embolic pulmonary hypertension (WHO Group 4), bosentan therapy led to significant reductions in PVR and improved dyspnoea score, while the 6MWD remained unchanged over the 6 month study period ('BosEntan in iNopErable Forms of chronic Thrombo-embolic pulmonary hypertension': BENEFIT).

## Ambrisentan

Ambrisentan is an orally active  $ET_A$ -receptor antagonist belonging to the propanoic acid class. Although data describing the selectivity of ambrisentan for the  $ET_A$  receptor vary between 29:1<sup>32</sup> and >4000:1,<sup>33</sup> depending on the assay cited, the drug is considered to be a selective  $ET_A$ -receptor antagonist.<sup>70,71</sup> In the USA, ambrisentan has been approved at a dose of 5–10 mg once daily for PAH patients with WHO functional class II or III symptoms to improve exercise capacity and delay clinical worsening. In Europe, ambrisentan was approved in April 2008 following a positive opinion from the European Committee for Human Medicinal Products for the treatment of PAH patients in functional class II and III.<sup>72</sup>

Results are based on a 12 week, blinded-to-dose (1, 2.5, 5, or 10 mg daily) Phase II study<sup>73</sup> (improvements in 6MWD, functional

class, Borg score, quality of life, and pulmonary haemodynamics) and two pivotal studies, 'AmbRIESentan in patients with moderate to severe PAH', ARIES-1<sup>74</sup> and ARIES-2,<sup>75</sup> that have not yet been published in full.

The long-term follow-up of patients treated with ambrisentan in the two pivotal studies and the open-label extension (ARIES-E,  $n = 383$ ) shows that 95% were alive at 1 year and 94% were still receiving ambrisentan monotherapy, with sustained efficacy for 6MWD, dyspnoea score, and functional class.<sup>76</sup>

## Sitaxentan

Sitaxentan sodium, a highly selective  $ET_A$ -receptor antagonist of the sulphonamide class of ETRA, has received approval for the treatment of PAH patients with WHO functional class III symptoms at an oral dose of 100 mg once daily (European Union, Canada, and Australia). The FDA has not approved sitaxentan to date, and another placebo-controlled study with sitaxentan is currently planned (STRIDE-5) to provide additional data.

The safety and efficacy of sitaxentan in patients with PAH has been clinically tested in the 'sitaxentan to relieve impaired exercise' (STRIDE) programme,<sup>70</sup> including three randomized, placebo-controlled pivotal trials (STRIDE-1,<sup>77</sup> STRIDE-2,<sup>78</sup> and STRIDE-4), two non-controlled studies (Study 211 and STRIDE-6),<sup>79</sup> and three long-term studies (STRIDE-1X, STRIDE-2X, and STRIDE-3).

Sitaxentan significantly improved functional class (STRIDE-1, STRIDE-2, STRIDE-4), 6MWD (STRIDE-1, STRIDE-2), dyspnoea score (STRIDE-1), and haemodynamics (Study 211, STRIDE-1). Improvements in time to clinical worsening could only be demonstrated in a *post hoc* meta-analysis using pooled data from the three pivotal studies.<sup>70</sup>

Long-term data are available from a small group of patients, suggesting that efficacy and safety are maintained for up to 12 months,<sup>80</sup> as well as preliminary data from the extension studies, with mean exposures of 26 (STRIDE-1X<sup>70</sup>) and 36 weeks (STRIDE-2X<sup>81</sup>).

Data from subgroup analyses did not exhibit a clinically relevant treatment effect in patients with PAH associated with CHD.<sup>70</sup> In contrast, the subgroup of patients with PAH associated with connective tissue disease (CTD) showed an increased 6MWD with sitaxentan treatment.<sup>82,83</sup>

## Endothelin-receptor selectivity and drug efficacy

The most frequent clinical endpoint used to assess drug efficacy in PAH has been exercise capacity, assessed by the 6MWD, although its appropriateness as a measure has been debated.<sup>84–86</sup> Moreover, as studies with ETAs have included different patient populations, it is difficult to judge, using any measure, whether  $ET_A$  selectivity provides a clinically important benefit for patients with PAH.

### 6-minute walk distance

Studying the evidence where 6MWD was used as a measure of efficacy, the placebo-corrected improvements from baseline to Week 12 (BREATHE-1<sup>62</sup> and ARIES-1<sup>74</sup>) or Week 18

**Table 3** Characteristics and main outcomes of pivotal studies for approved endothelin receptor antagonists

	<b>Bosentan</b>		<b>Sitaxentan</b>		<b>Ambrisentan</b>	
	<b>Study 351 (Channick et al.<sup>61</sup>)</b>	<b>BREATHE-1 (Rubin et al.<sup>62</sup>)</b>	<b>STRIDE-1 (Barst et al.<sup>77</sup>)</b>	<b>STRIDE-2 (Barst et al.<sup>78</sup>)</b>	<b>ARIES-1 (Oudiz et al.<sup>74</sup> and PI)</b>	<b>ARIES-2 (Olschewski<sup>108</sup> and PI)</b>
Selectivity	Oral ET <sub>A</sub> /ET <sub>B</sub> antagonist	Oral ET <sub>A</sub> /ET <sub>B</sub> antagonist	Oral highly selective ET <sub>A</sub> antagonist	Oral highly selective ET <sub>A</sub> antagonist	Oral selective ET <sub>A</sub> antagonist	Oral selective ET <sub>A</sub> antagonist
Drugs and daily dosages in the study	Placebo/bosentan 125–250 mg	Placebo/bosentan 250 mg/ bosentan 500 mg	Placebo/sitaxentan 100 mg/ sitaxentan 300 mg	Placebo/sitaxentan 50 mg/ sitaxentan 100 mg/ bosentan <sup>d</sup>	Placebo/ambrisentan 5 mg/ ambrisentan 10 mg	Placebo/ambrisentan 2.5 mg/ ambrisentan 5 mg
Setting	US and EUR	US and EUR	US (and 1 centre in Canada)	US and EUR	US and EUR	US and EUR
Dosing regimen	2 × /day	2 × /day	1 × /day	1 × /day	1 × /day	1 × /day
Study details at inclusion/baseline characteristics						
Study duration post-randomization (weeks)	12	16	12	18	12	12
Inclusion range for age (years)	≥ 18	≥ 12	≥ 16–75	12–78	≥ 18	≥ 18
Baseline 6 min walk distance for inclusion (m)	≥ 150 and ≤ 500	≥ 150 and ≤ 450	Not defined (only second endpoint)	≥ 150 and ≤ 450	≥ 150 and ≤ 450	≥ 150 and ≤ 450
PAH aetiology	IPAH (81%), PAH-SSc (19%) in bosentan group	IPAH (71%), PAH-SSc (23%), PAH-Lupus (6%)	IPAH (53%), PAH-CTD (24%), PAH-CHD (24%)	IPAH (59%), PAH-CTD (30%), PAH-CHD (11%)	IPAH (63%), PAH assoc. with CTD, HIV, anorexigen (37%)	IPAH (65%), PAH assoc. with CTD, HIV, anorexigen (35%)
WHO functional class	III (100%)	III (90%), IV (10%)	II (33%), III (66%), IV (1%)	II (37%), III (59%), IV (4%)	I (3%), II (32%), III (58%), IV (7%)	I and II (46%), III and IV (54%)
Patient disposition	36 screened, 32 randomized (2:1). No discontinuations	Screened: n.r., 213 randomized (1:1:1), 14 discontinued	Screened: n.r., 178 randomized (1:1:1), 12 discontinued	Screened: n.r., 247 randomized (1:1:1:1), 31 discontinued	Screened: n.r., 202 randomized (1:1:1), discontinuation n.r.	Screened: n.r., 192 randomized (1:1:1), discontinuation n.r.
Males:females (%)	19:81 (bosentan)	29:71 (bosentan)	21:79	22:78	n.r.	n.r.
Mean age (years)	52 (33–73) (bosentan)	49 (13–80)	46 (17–74)	54 (14–78)	n.r.	n.r.
Mean 6 min walk distance at baseline (m)	360 (± 86) (bosentan)	330 (± 74)	398 (± 110)	337 (± 80)	341 (± 76)	348 (± 84)
mPAP (mmHg)	54 (± 13) (bosentan)	55 (± 16)	54 (± 15)	48 (± 14)	n.r.	n.r.

## Results at study end in the treatment groups

6 min walk distance (m) <sup>a</sup>	- 6/70*	- 8/27*/47**	- 13/22**/20**	- 6.5/17.8/24.9/23.0	- 7.8/22.8**/43.6***	- 10.1/22.2*/49.4***
mRAP (mmHg)	4.9/ - 1.3**	n.a.	1/0*	n.a.	n.a.	n.a.
mPAP (mmHg)	5.1/ - 1.6 *	n.a.	0 / - 3 / - 5***	n.a.	n.a.	n.a.
Cardiac output (L/min)	- 0.5/0.5*** (CI)	n.a.	0.0/0.3/0.4*** (CI)	n.a.	n.a.	n.a.
PVR (dyn s cm <sup>-5</sup> )	191/ - 223***	n.a.	49/ - 221/ - 194***	n.a.	n.a.	n.a.
Median change in peak VO <sub>2</sub> (mL O <sub>2</sub> /kg/min) <sup>b</sup>	n.a.	n.a.	0.0/0.5/3.1**	n.a.	n.a.	n.a.
Improvement in Borg dyspnoea index	1.4/ - 0.2	0.3/ - 0.1/ - 0.6	n.r.	0.2/n.r./0.0/n.r.	Ambrisentan yes: details n.r.	Ambrisentan yes: details n.r.
Improvement in WHO functional class (%)	9/43	30/43/41	15/29/30	Sitaxentan 100 mg signif.	Ambrisentan yes: details n.r.	Ambrisentan yes: details n.r.
Time to clinical worsening	Sign. improved vs. placebo	Sign. improved vs. placebo	n.r.	Sitaxentan 100 mg n.s. (trend to improv.)	Pl: significantly delayed (pooled)	Pl: significantly delayed (pooled)
Incidence of clinical worsening (n)	27/0*	14/5/4	5/0/2	10/6/4/9	Placebo 7 (10%)/ ambrisentan pooled 4 (3%)*	Placebo 13 (22%)/ ambrisentan pooled 8 (6%)*
LFT elevations >3 × ULN (%)	0/6.3	3/4/14	3/0/10	6/5/3/11	3/0/0	2/0/0
Peripheral oedema (%)	5/8 <sup>c</sup>	5/8 <sup>c</sup>	17/16/25	8/8/11/15	10 (placebo), 27 (5+10 mg pooled)	6/8/13

n.a., not applicable (i.e. not done in the study); n.r., not reported; bos, bosentan group only; CI, cardiac index; CHD, congenital heart disease; CTD, connective tissue disease; L, litres; LFT, liver function tests; mPAP, mean pulmonary arterial pressure; Pl, Letairis (ambrisentan) prescribing information (in the US); PVR, pulmonary vascular resistance; ULN, upper limit of normal; VO<sub>2</sub>, oxygen uptake; WHO, World Health Organization.

<sup>a</sup>Primary endpoint in all studies with exception of STRIDE-1.

<sup>b</sup>Primary endpoint in STRIDE-1.

<sup>c</sup>Data reported for pooled PAH studies in Tracleer® European Public Assessment Report (EPAR).

<sup>d</sup>Open-label bosentan arm at the standard dose, i.e., 62.5 mg orally b.i.d. for 4 weeks, then increasing to the maintenance dose of 125 mg b.i.d.

Statistics vs. placebo: \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

(STRIDE-2<sup>78</sup>) were +35, +51, and +31 m for bosentan, ambrisentan, and sitaxentan, respectively (Table 3). A direct comparison is difficult, as BREATHE-1 included only patients in functional class III and IV while ARIES-1 and STRIDE-2 included  $\geq 35\%$  of patients in functional class I and II.

## Time to clinical worsening

Significant improvements in the time to clinical worsening have also been reported for all three ETRAs discussed. In BREATHE-1, both the time to and the incidence of clinical worsening were significantly reduced with bosentan compared with placebo.<sup>62</sup> In ARIES-1,<sup>74</sup> and ARIES-2,<sup>75</sup> the differences between ambrisentan and placebo with respect to incidence of and time to clinical worsening reached statistical significance. In a *post hoc* meta-analysis pooling 512 patients from STRIDE-1, STRIDE-2, and STRIDE-4, significant improvements in time to clinical worsening were seen in patients treated with sitaxentan 100 mg daily compared with placebo;<sup>70</sup> this is in contrast to the individual STRIDE-1<sup>77</sup> and STRIDE-2<sup>78</sup> studies, where statistical significance was not reached.

## Haemodynamics

Since ET<sub>A</sub> and ET<sub>B</sub> receptors counter-regulate vascular tone, variations in receptor selectivity could result in different haemodynamic profiles.

The haemodynamic changes from baseline to Week 12 for bosentan and sitaxentan are shown in Table 3. Despite differing study populations, both drugs equally reduced PVR by an average of 220 dynes s cm<sup>-5</sup> following a 3 month treatment period; comparable with the decrease of 226 ± 202 dynes s cm<sup>-5</sup> reported for ambrisentan.<sup>73</sup> Small differences in favour of less-selective ETRAs were observed with respect to right atrial pressure reductions.

Haemodynamic superiority of selective ET<sub>A</sub> blockade, theoretically mediated by unblocked ET<sub>B</sub> receptors, cannot be inferred from these data. Likewise, non-selective ETRA blockade does not seem to be associated with clear haemodynamic advantages when indirectly compared with selective blockade.

## Survival

There is no definitive study proving a survival benefit for any ETRA, owing to the fact that long-term, placebo-controlled studies are perceived as ethically unjustifiable. Therefore, survival rates for new PAH therapies are generally compared with historical survival rates from patients not receiving PAH-specific drug treatment.<sup>87</sup>

For patients enrolled in the two placebo-controlled bosentan trials and subsequently followed up for a mean of 2.1 ± 0.5 years, survival estimates were 96 and 89% at 12 and 24 months, compared with a predicted survival of 69 and 57%, respectively.<sup>63</sup> At the end of 12 and 24 months, 85 and 70% of patients, respectively, remained on bosentan monotherapy. Another retrospective analysis of 103 consecutive IPAH patients treated with first-line bosentan therapy reported overall survival estimates of 92, 89, and 79% at 1, 2, and 3 years, respectively, compared with a predicted survival of 71, 61, and 51% at these time points<sup>64</sup> (85 and 70% on monotherapy at 12 and 24 months,

respectively). In this group, 44% of patients received additional intravenous epoprostenol therapy during follow-up.

For ambrisentan, an integrated analysis of 383 PAH patients in ARIES-I, ARIES-2, or ARIES-E reported an 1 year survival of 95%.<sup>76</sup> During long-term, open-label treatment (mean, 1.7 years) of 64 PAH patients treated with ambrisentan, survival in the IPAH subgroup was 89% (67% on monotherapy) compared with a predicted survival of 66%.<sup>88,89</sup>

Survival data for sitaxentan are available from the STRIDE-2X programme for 145 patients with PAH treated with sitaxentan 100 mg/day.<sup>81</sup> At 1 year, survival estimates were 96% for the PAH group and 98% for the subgroup of patients with PAH and CTD. In both groups, additional PAH therapies had been added during this period in 13 and 10% of the patients, respectively.

From these data, differential effects on survival with any of the ETRAs discussed cannot be inferred.

## Comparative trials

A unique data set is provided by the STRIDE-2 trial, in which 245 patients were randomized to placebo, sitaxentan (50 or 100 mg q.d.), or bosentan (62.5 mg b.i.d. for 1 month followed by 125 mg b.i.d.).<sup>78</sup> The bosentan arm was, however, open label and included only as a comparator arm (events were rater-blinded). At 18 weeks, both sitaxentan 100 mg and bosentan arms showed significant increases in 6MWD, the primary endpoint. Improvements in functional class (secondary endpoint) were observed with sitaxentan 100 mg ( $P = 0.04$ ). Time to clinical worsening did not improve with either treatment.

After 18 weeks, patients were entered into the extension study STRIDE-2X where patients who received sitaxentan (100 mg) or bosentan during STRIDE-2 continued on their respective therapies, in an open-label fashion. Patients receiving sitaxentan 50 mg daily during STRIDE-2 had their dosages increased to 100 mg daily, and the patients on placebo were assigned to sitaxentan (100 mg daily) or bosentan. Preliminary results of pre-specified analyses for patients treated for up to 1 year (bosentan,  $n = 84$ ; sitaxentan,  $n = 145$ ) revealed differences between the treatment arms, with better outcomes for the sitaxentan-treated patients when compared with bosentan therapy in parameters such as risk of discontinuation of monotherapy (25 vs. 45%,  $P = 0.003$ ) and abnormal liver enzyme levels (4 vs. 14%,  $P = 0.01$ ). However, no significant differences between both treatment regimens were observed for functional class, 6MWD, or survival.<sup>81</sup> Thus, no clinically meaningful differences between these drugs with respect to selectivity-related efficacy were observed.

## Selectivity and safety

### Clinical side effects

Although ETRAs are generally well tolerated, they are associated with side effects related to their vasodilatory properties including peripheral oedema, headache, and palpitations. Table 4 provides an overview on the incidence of those side effects that have the greatest relevance in everyday clinical care.

### Abnormal liver function tests

The most clinically relevant side effects reported with ETRA therapy are dose-dependent liver function abnormalities. These present as elevated transaminases and/or bilirubin levels, and are seen more frequently with the sulfonamide-class ETAs. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly thereafter. It has been reported that bosentan inhibits the bile salt export pump, which may lead to cholestatic liver injury as a result of the intracellular accumulation of bile salts, while increasing bile salt-independent bile flow.<sup>90,91</sup> While the incidence of hepatotoxicity in the placebo-controlled trials was highest with bosentan (Tables 2 and 4), the inclusion criteria and control group characteristics of the studies should be taken into account. While patients with liver enzyme elevations  $>1.5\times$  upper limit of normal (ULN) at baseline were excluded from ARIES-1, ARIES-2, and STRIDE-2, patients with elevations up to  $3\times$  ULN were included in STRIDE-1 and BREATHE-1. Similarly, the incidence of hepatic aminotransferase elevations  $>3\times$  ULN in the control groups varied between 0 and 6% (Table 3).

Consequently, drug surveillance programmes (named TRAcleer eXcellence Post-Marketing Surveillance Programme, TRAX, for bosentan, Thelin Outcomes for Patients Surveillance, TOPS, for sitaxentan, and VOLibris Tracking, VOLT, for ambrisentan) had/have to be conducted in the first years after introduction for all ETAs. In the USA, the marketed drugs (bosentan and ambrisentan) can only be prescribed in the frameworks of special restricted distribution programmes.

It is a useful finding that in case of elevated transaminases, a switch to another ETRA may be an option. The STRIDE-6 study<sup>79</sup> aimed to explore the potential use of sitaxentan in PAH patients who previously discontinued bosentan treatment (13 patients owing to 'safety issues', 12 patients with aminotransferase

elevations, and one patient with rash). Among the 12 patients with liver enzyme elevations on bosentan treatment, only one individual re-developed this side effect during 12 weeks of sitaxentan therapy. An open-label study of ambrisentan evaluated the hypothesis that patients previously discontinued from bosentan (86%), sitaxentan (6%), or both (8%) because of elevations in hepatic aminotransferases can be successfully treated with ambrisentan without recurrence of hepatotoxicity. None of these 36 patients developed recurrent liver transaminase elevations during the initial 12 week observation period.<sup>92</sup> In conclusion, among the various ETAs currently available for the treatment of patients with PAH, receptor selectivity itself does not appear to be related to the incidence of hepatotoxicity. It is likely that chemical properties of the drugs, the pharmacokinetics or drug–drug interactions, or patient characteristics, may influence the incidence and severity of the side effects rather than differences in ET-receptor selectivity.

### Decreased haemoglobin

Owing to an as yet incompletely identified mechanism, potentially related to vasodilatation and subsequent fluid shift producing haemodilution, all ETAs are associated with a usually modest, dose-dependent, and partially transient reduction in haemoglobin levels. Decreases in haemoglobin were not related to haemolysis, bone marrow depression, or risk of bleeding. They occur in about 5–7% of patients, irrespective of the ETRA used. Haemoglobin (and haematocrit) reductions are likely to be a dose-dependent class effect of the ETAs that may not be attributable to receptor selectivity.

For all three agents, these symptoms typically do not require discontinuation of therapy or dose adjustment and are usually not dose dependent (up to the approved doses). The occurrence, frequency, and severity of these side effects appear not to be related to the degree of selectivity for the ET<sub>A</sub> receptor.

**Table 4** Frequent side effects of the three endothelin receptor antagonists in pulmonary arterial hypertension patients according to labelling

Side effect	Sitaxentan	Bosentan	Ambrisentan
ALT/AST elevations	$>3\times$ ULN: 7% for sitaxentan 100 mg/day treated patients ( $n = 887$ ) vs. 5% of PBO-treated patients ( $n = 155$ ). $>5\times$ ULN: 4% (36/887) for sitaxentan 100 mg/day vs. 0.6% in the PBO group (1/155).	$>3\times$ ULN: eight integrated PBO-controlled studies (six other than PAH): 11.2% of the bosentan vs. 1.8% of the PBO-treated patients. In PAH: 11.6% for bosentan 125 mg b.i.d., and 14.3% for bosentan 250 mg twice daily. $>8\times$ ULN: 2.1% for bosentan 125 mg b.i.d. vs. 7.1% for 250 mg twice daily.	$>3\times$ ULN: 0.8% for ambrisentan vs. 0.2% PBO $>8\times$ ULN 0.2% for ambrisentan vs. 0% for PBO.
Peripheral oedema	9%	PBO-controlled studies 4.7 vs. 1.4% PBO BREATHE-5 study: 18.9 vs. 5.9% PBO BREATHE-4 study 31% (no PBO comparison) RAPIDS-1, -2: 14 vs. 5% PBO	17% (PBO-adjusted 6%)
Headache	15%	PBO-controlled studies 15.8 vs. 12.8% PBO BREATHE-5 study: 13.5 vs. 11.8% PBO BREATHE-4 study 19% (no PBO comparison)	15% (PBO-adjusted 1%)
Decreased haemoglobin	7% (PBO-adjusted 4%)	5.6 (PBO-adjusted 3.0%)	7% (PBO-adjusted 3%)

Source: Product information (Summary of Product Characteristics, SmPC) of Tracleer, Thelin, and Letairis. ALT, alanine aminotransferases; AST, aspartate aminotransferases; ULN, upper limit of normal; PBO, placebo.

## Peripheral oedema

There has been speculation as to whether peripheral oedema occurs more frequently as a drug-specific, ET<sub>B</sub>-mediated side effect. However, the incidences of leg oedema in the pivotal ETRA studies (Table 4) suggest that the incidence is related to patient characteristics (as can be derived from the large variance in the placebo groups), but do not suggest a significant drug-related effect. Notably, a warning label has been issued by the FDA for ambrisentan based on post-marketing reports of fluid retention occurring within weeks after starting ambrisentan.<sup>71</sup>

## Selectivity and PAH associated with connective tissue disease

Of the wide spectrum of diseases encompassed by the term 'pulmonary hypertension', PAH with associated CTD (PAH-CTD) is a disease for which patients have a particularly poor prognosis. Importantly, this subgroup has been included in several trials evaluating ETAs; however, the clinical relevance of ET-receptor selectivity in this patient group has not been specifically explored.

The BREATHE-1 trial included 47 patients with systemic sclerosis (22%).<sup>62</sup> In contrast to patients with IPAH, bosentan did not significantly increase 6MWD. However, the decline in walking distance of 40 m at 16 weeks in the systemic sclerosis placebo group ( $n = 14$ ) was prevented by bosentan (+3 m,  $n = 33$ ).

For ambrisentan, comparable efficacy with respect to functional capacity, measured as 6MWD, was described for 19 patients (30%) with PAH associated with collagen vascular disease, when compared to patients with idiopathic PAH.<sup>73</sup>

A *post hoc* analysis of 42 patients with PAH-CTD enrolled in the STRIDE-1 study<sup>83</sup> showed that during the 12 week placebo-controlled phase, sitaxentan (pooled 100 and 300 mg groups) increased the placebo-subtracted 6MWD by 58 m ( $P = 0.027$ ), improved haemodynamics, as well as certain domains within the quality-of-life assessment. Notably, in contrast to the bosentan data, sitaxentan not only prevented deterioration of exercise capacity but also significantly improved 6MWD by 20 m ( $P = 0.037$ ), compared with baseline. In another *post hoc* meta-analysis pooling 512 patients from STRIDE-1, STRIDE-2, and STRIDE-4, a subgroup of 129 patients with PAH-CTD was analysed. Within this subgroup, 39 patients treated with sitaxentan 100 mg daily showed a significantly improved 6MWD by 38 m ( $P = 0.0419$ ), compared with placebo.<sup>70</sup> This effect was not seen with sitaxentan 50 or 300 mg daily in this PAH subgroup.

## Long-term outcomes in PAH-CTD

Retrospective analyses have been published examining the long-term effects of ETAs in patients with PAH-CTD. In two randomized, controlled studies investigating bosentan in PAH,<sup>61,62</sup> 66 patients with PAH-CTD were randomized to receive either bosentan ( $n = 44$ ) or placebo ( $n = 22$ ). Forty-four patients on bosentan were stable in 6MWD at study end, while the placebo patients deteriorated; the placebo-subtracted difference was 22 m (non-significant). Subsequently, in an open-label, long-term extension study ( $1.6 \pm 0.9$  years), survival rate in the 64 patients receiving bosentan was 86% after 1 year and 73% after 2 years.<sup>93</sup> These

outcome data are comparable with the 81 and 71% survival rates at 1 and 3 years, respectively, seen among 45 patients with PAH associated with scleroderma, treated with bosentan (mono- or combination therapy), as detailed in the Royal Free Hospital registry. These findings compare favourably to the 68 and 47% survival rates at 1 and 2 year, respectively, in a historical cohort of 47 patients in the same institution treated with conventional therapy.<sup>94</sup>

Within the STRIDE-2X study, 52 patients with PAH-CTD (scleroderma,  $n = 38$ ; overlap syndrome,  $n = 9$ ; lupus,  $n = 5$ ) were included. According to a preliminary report,<sup>82</sup> for this subgroup, time to discontinuation owing to adverse events or elevated hepatic aminotransferase, time to clinical worsening, and 1 year survival were all improved with sitaxentan therapy compared with placebo. In the STRIDE-1X study, at the end of the blinded extension phase, following mean treatment duration of 26 weeks, significantly more patients were in functional class I or II with sitaxentan, compared with baseline.<sup>70</sup>

Taken together, these data document short- and long-term clinical efficacy for ETAs in the subgroup of patients with PAH-CTD. When comparing these *post hoc* analyses, an advantage of selective ET<sub>A</sub> blockade appears possible, since some of the efficacy endpoints reached statistical significance only with sitaxentan treatment. Differential effects on survival with these ETAs cannot be evaluated from these data.

## Drug metabolism, drug interactions, and combination therapy

Bosentan, ambrisentan, and sitaxentan have divergent pharmacological and pharmacokinetic characteristics, resulting in clinically important differences with respect to drug metabolism, drug interactions, and their potential for use in combination therapy (Table 2). Of interest are the interactions of bosentan with sildenafil, a frequently used combination therapy, where sildenafil plasma levels are reduced by about 50% while bosentan concentrations rise by approximately 50%.<sup>95,96</sup> Theoretically, sub-therapeutic sildenafil levels as well as increased bosentan-related liver toxicity may result. However, in clinical practice, this combination is well tolerated and appears to be effective.<sup>97</sup> No such interaction with sildenafil has been described for ambrisentan or sitaxentan.

Other important co-medications in patients with PAH are vitamin-K antagonists. Bosentan and sitaxentan have different effects on the doses of oral anticoagulants (vitamin-K antagonists): bosentan partially induces the cytochrome P450 system, thereby increasing warfarin metabolism and the required dose.<sup>98,104</sup> In contrast, sitaxentan inhibits the liver isoenzyme CYP2C9. Thus, combining sitaxentan and warfarin in healthy volunteers can lead to a 2.4-fold increase in exposure to warfarin, therefore, requiring a substantial reduction in dose (~80%) at initiation of therapy to avoid bleeding complications.<sup>99</sup> No such interaction occurs with ambrisentan; however, according to the labelling, the drug interaction potential of ambrisentan 'has not been well characterized'.<sup>71</sup>

In summary, most of these characteristics are related to the class of drug and differences in metabolism instead of reflecting differences in ET-receptor selectivity.

## Conclusions

Together, these data, derived mainly from a series of randomized, controlled trials and their open-label extensions, confirm that ET antagonism is an effective and generally well-tolerated treatment option for patients with symptomatic PAH. They represent a major advance within the available therapeutic armamentarium for this severely compromised patient population.

Considering the entire group of PAH patients who have been prospectively studied in these trials, a clinically meaningful difference between the three approved ETAs with respect to their ET-receptor selectivity could not be demonstrated to date. Therefore, in clinical practice, other features are likely to be of greater relevance when considering treatment, such as the potential for serious drug–drug interactions, convenience of dosing schedule, or rates of limiting side effects. These characteristics bear more relation to the chemical or pharmacological properties of the drug than to receptor selectivity itself.

Another important limitation of the data discussed in this paper relates to the design of the studies. As mentioned earlier, ET-1 creates short-term effects, mainly vasoconstriction, as well as medium and long-term sequelae such as proliferation, inflammation, and fibrosis. Most of the studies discussed in this paper investigated the effects of pharmacological interventions over the periods of 12–16 weeks, thereby assessing only the short-term vasodilator potential of the drug under study.<sup>100</sup> From this perspective, the agents examined all resulted in a small, though significant change in exercise capacity over 12–16 weeks, irrespective of the drug used.<sup>86</sup> Considering these limitations, much longer follow-up periods and probably other endpoints might be necessary to detect clinically important differences related to receptor selectivity when comparing different ETAs. Until the results from such long-term trials become available, other strategies can be used to acquire data on the effects of different ETAs in the treatment of patients with PAH. As one of these projects, the ‘Comparison of Endothelin Receptor Antagonist therapy in routine care’ (ComPERA, <http://compera.org/>) has recently been initiated in the European Union. This prospective large-scale register documents safety and efficacy parameters in consecutive pulmonary hypertension patients treated with any of the approved ETAs (as mono- or combination therapy). These data should contribute to the optimization of the current ETA-based drug therapy and provide further insight into selectivity-related differences among the currently available drugs.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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