

# Targeted Oral Therapies in the Treatment of Pulmonary Arterial Hypertension

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## Abstract

Recent advances in our understanding of the pathophysiology of pulmonary arterial hypertension (PAH) have led to the US FDA's approval of eight drugs for its treatment. Although guidelines for the use of PAH therapies are available and regularly updated, there is a lack of information on how these agents differ and what characteristics may enable one agent to be of greater relative clinical utility than another. Oral agents may be compared across a variety of measures, including clinical efficacy, safety and tolerability, dosing and pharmacology, potential for drug interactions, treatment adherence and suitability for use in combination regimens. Although no large, prospective, head-to-head trial has been conducted with oral agents for PAH, data from placebo-controlled studies indicate that the enrolled patient populations were remarkably homogeneous with respect to demographic and disease severity parameters. In general, data suggest that these agents improve functional capacity, delay disease progression and improve haemodynamics. Additionally, long-term sustainability of response has been demonstrated. However, there was no consistently superior agent across the primary and secondary endpoints

assessed in these trials, and the magnitudes of improvements were in a fairly defined range across agents. Consequently, treatment choice may shift to other aspects such as drug safety and tolerability, potential for drug interactions, dosing convenience, treatment adherence, effect on quality of life and access to medication. In this review, the four targeted oral agents approved for the treatment of PAH in the US are reviewed, and clinical results are placed into context.

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries characterized by vasoconstriction, aberrant vascular proliferation and remodeling.<sup>[1]</sup> This causes a progressive increase in pulmonary vascular resistance (PVR), elevated pressure in the pulmonary circulation, and, ultimately, right ventricular failure and premature death. The pathophysiology of PAH is complex and incompletely understood; however, the pathological changes appear to result, at least in part, from an imbalance between mediators of vasodilation (e.g. prostacyclin, nitric oxide [NO]) and vasoconstriction (e.g. endothelin [ET]-1) in favour of the vasoconstrictive forces, and promotion of vascular smooth muscle cell proliferation in the pulmonary arteries. Levels of endogenous mediators of vasodilatory and antiproliferative effects are low in patients with PAH. The current therapies for PAH aim at mediating these vasodilatory and antiproliferative effects.

The goals of treatment of PAH are to relieve symptoms, increase the capacity to be active, and prolong survival. Optimal management of PAH includes: implementation of lifestyle and preventative measures; use of conventional therapy such as calcium channel blockers (calcium channel antagonists), anticoagulants, diuretics and digoxin; and treatment with targeted PAH medications. Before the development of PAH-specific therapies, the median survival time of patients with idiopathic PAH (IPAH) receiving conventional therapies was 2.8 years after diagnosis.<sup>[2]</sup> Results from a US national prospective registry published in 1991 revealed survival rates of 68%, 48% and 34% at 1, 3 and 5 years, respectively.<sup>[2]</sup> However, recent advances in the understanding of the pathophysiological and molecular mechanisms that underlie PAH have led to the development of new targeted

therapies and apparent improved survival rates. Survival data from a large, contemporary registry in France reported 1-year survival of 88% among patients with IPAH, familial PAH or associated PAH.<sup>[3]</sup> A recent study observed contemporary survival in patients with IPAH, familial PAH and anorexigenic-associated PAH of 92%, 75% and 66%, at 1, 3 and 5 years, respectively, which was significantly higher than survival rates predicted by the US National Institutes of Health risk stratification equation.<sup>[4]</sup> The New York Heart Association (NYHA) functional class (FC) at time of diagnosis is a strong predictor of survival, with higher symptom severity associated with worse outcomes.<sup>[2]</sup>

Targeted therapies for the treatment of PAH include prostacyclin analogues administered by intravenous, inhaled and subcutaneous routes; oral ET receptor antagonists (ERAs); and oral phosphodiesterase 5 (PDE-5) inhibitors.<sup>[5-7]</sup> More recently, the oral ERAs bosentan and ambrisentan<sup>[8]</sup> and the PDE-5 inhibitors sildenafil and tadalafil<sup>[9]</sup> have demonstrated significant benefits in the treatment of PAH.

In an effort to help direct therapy given the myriad of currently available treatment options, the American College of Chest Physicians guidelines recommend treatment based on variables assessing patients' disease severity and risk, including but not limited to FC.<sup>[10,11]</sup> The new evidence-based treatment algorithm recommends that patients who are not candidates for calcium channel blocker therapy should consider alternative therapies based on their FC.<sup>[12]</sup> Typically, patients with FC II or III symptoms are initiated on an oral agent, with prostacyclins reserved for sicker patients or for those patients who achieve a suboptimal response or who are declining on oral monotherapy

or combination therapy. As of this writing (July 2010), first-line targeted oral therapy options include bosentan, ambrisentan, sildenafil and tadalafil. Although none of the four oral agents have been directly compared in a large, prospective, randomized, active-comparator trial, there may be compelling differences between these agents in clinical efficacy and safety, pharmacology and dosing convenience, treatment adherence, potential for drug interactions, effect on quality of life, access to medication, and suitability for use in combination regimens.

The clinical profiles of four currently approved targeted oral agents in the treatment of patients with PAH – bosentan, ambrisentan, sildenafil and tadalafil – are highlighted in this review. These agents have distinct pharmacological and clinical profiles, which may make some agents more suitable for different clinical settings. The current evidence from clinical studies was obtained by performing a thorough literature search of PubMed from January 2000 to December 2009 using the general search terms ‘pulmonary arterial hypertension’ and ‘bosentan’, ‘ambrisentan’, ‘sildenafil’ or ‘tadalafil’.

## 1. Mechanisms of Action

Three major pathways – ET, NO and prostacyclin – are known to be involved in the pathogenesis of PAH, and targeted therapies have been developed for each pathway. Two of the pathways are established targets of oral therapies.

### 1.1 Endothelin Receptor Antagonists

ET-1, a peptide produced in endothelial cells and vascular smooth muscle cells, binds and activates two distinct, G protein-coupled receptor isoforms, ET<sub>A</sub> and ET<sub>B</sub>. Whereas ET<sub>A</sub> is located predominantly on smooth muscle cells, ET<sub>B</sub> is found on both endothelial and vascular smooth muscle cells.<sup>[1,8,13,14]</sup> Activation of the ET<sub>A</sub> receptor on smooth muscle cells causes sustained vasoconstriction and proliferation of these cells. However, activation of ET<sub>B</sub> on endothelial cells induces clearance of ET-1 from the circulation and mediates vasodilation through the activation of NO

and prostacyclin. ET-1 is overexpressed in PAH and is thought to be important in the pathogenesis of the disease.<sup>[12]</sup> Therefore, antagonists to ET receptors were developed as targeted PAH therapy agents.

Bosentan, the first ERA, is considered a non-selective competitive antagonist of the ET<sub>A</sub> and ET<sub>B</sub> receptors, and ambrisentan is referred to as an ET<sub>A</sub>-selective antagonist. Based on an *in vitro* competitive receptor binding assay, bosentan and ambrisentan have a relative affinity for ET<sub>A</sub> over ET<sub>B</sub> of 20 : 1 and 77 : 1, respectively.<sup>[15]</sup> When affinities were assayed using human myocardial membranes, bosentan and ambrisentan had >240-fold and >4000-fold higher affinity for ET<sub>A</sub> over ET<sub>B</sub>, respectively.<sup>[16,17]</sup> According to one theory, ambrisentan should selectively block the vasoconstrictive effects of ET<sub>A</sub> while maintaining the vasodilatory and ET-1-clearing properties of the ET<sub>B</sub> receptor. Despite an apparent receptor selectivity advantage for ambrisentan, a clinically meaningful or consistent difference in efficacy between these two agents has been difficult to demonstrate.<sup>[14]</sup> Therefore, other factors such as adverse events and drug interactions may be more relevant when considering treatment with ERA agents.

### 1.2 Phosphodiesterase 5 Inhibitors

PDEs are a superfamily of enzymes that inactivate cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate, the second messengers of NO and prostacyclin, respectively.<sup>[1]</sup> Production of NO is impaired in patients with PAH,<sup>[18]</sup> resulting in decreased production of cGMP. One strategy in the treatment of PAH is to prolong the circulation of existing cGMP by inhibiting its inactivation by PDEs. Because PDE-5 is the predominant and selective PDE in pulmonary tissue,<sup>[19]</sup> PDE-5 inhibitors increase cellular cGMP levels causing preferential pulmonary vasodilation with minimal reductions in systemic blood pressure. Sildenafil and tadalafil are PDE-5 inhibitors that have similar mechanisms of action but exhibit different selectivity for the various PDEs.<sup>[20]</sup> Both sildenafil and tadalafil have higher selectivity for PDE-5 than for PDE-1, PDE-2, PDE-3 and PDE-4, at a level of 80- to >1000-fold

for sildenafil and >10 000-fold for tadalafil. However, sildenafil has relatively lower (10-fold) PDE-5 selectivity versus PDE-6, which is expressed in the retina.<sup>[20]</sup> In contrast, tadalafil has an approximately 700-fold higher selectivity for PDE-5 than for PDE-6 and may be less likely to cause some ophthalmological adverse effects.<sup>[20]</sup> However, tadalafil is more selective for PDE-11 relative to PDE-5 compared with sildenafil.<sup>[21]</sup> Since PDE-11 is localized predominantly in skeletal muscles, back pain and myalgia can occur more frequently with tadalafil than with sildenafil treatment.<sup>[22]</sup>

Although the currently approved therapies for the treatment of PAH function through different modes, the pathways are not distinct and are thought to interact with one another in a complex manner that has yet to be fully elucidated. Prosta-cyclin and NO are also known to reduce the release of ET-1, thus controlling the signaling for ET receptors.<sup>[13]</sup> Together these complex interactions promote aberrant cellular growth, vasoconstriction and thrombosis within the pulmonary arteries.

## 2. Pharmacology of Targeted Oral Pulmonary Arterial Hypertension (PAH) Therapies

Pharmacological and pharmacokinetic properties are divergent among the oral PAH agents, resulting in clinically important differences with

respect to dosing, metabolism, the potential for drug interactions and use in combination therapy (table I).<sup>[14,21,23,24]</sup>

### 2.1 Pharmacokinetics

Among the four approved oral agents, sildenafil is the most rapidly absorbed agent, with maximum plasma concentrations observed after ~1 hour in the fasted state, but this rate of absorption is slowed when taken with food. Sildenafil and bosentan have shorter elimination half-lives ( $t_{1/2}$ ), necessitating more frequent dosing (three times daily [tid] and twice daily [bid], respectively). In contrast, tadalafil and ambrisentan exhibit  $t_{1/2}$  values of 17.5 hours and 15 hours, respectively, which allows convenient once-daily (od) dosing.

### 2.2 Drug Metabolism

The four agents are primarily metabolized by hepatic cytochrome P450 (CYP) isoenzymes.<sup>[14,23]</sup> Consequently, drugs that are substrates of or inhibit or induce these isoenzymes can potentially be involved in drug interactions when co-administered with the oral agents for PAH (table II).<sup>[16,25-27]</sup> Isoenzyme CYP3A4 is implicated in the metabolism of all four agents to different extents. Therefore, these agents have drug interactions with inhibitors of CYP3A4 such as ketoconazole, itraconazole, ritonavir and erythromycin, and with inducers of

**Table I.** Comparison of pharmacological properties of oral agents for pulmonary arterial hypertension

Parameter	PDE-5 inhibitors		ERA	
	tadalafil <sup>[21,23,24]</sup>	sildenafil <sup>[21,23]</sup>	ambrisentan <sup>[14]</sup>	bosentan <sup>[14]</sup>
Individual dose (mg)	40	20	5–10	62.5–125
Frequency of administration	od	tid	od	bid
$t_{max}$ (h)	2	1	1.7–3.3	3–5
Dose linearity	Yes <sup>a</sup>	No	Yes	Yes
$t_{1/2}$ (h)	17.5	3–5	15	5.4
Time to steady state (d)	5	NA	3–4	3–5
Food effect	No	Yes	No	No
Metabolism	Hepatic (CYP)	Hepatic (CYP)	Hepatic (CYP and glucuronidation)	Hepatic (CYP)
Main CYP involved in drug metabolism	CYP3A4	CYP3A4, CYP2C9	CYP3A4, CYP2C19	CYP2C9, CYP3A4

a Linearity demonstrated through 20 mg/d.

**bid** = twice daily; **CYP** = cytochrome P450 enzyme; **ERA** = endothelin receptor antagonist; **NA** = not available; **od** = once daily; **PDE-5** = phosphodiesterase 5; **tid** = three times daily;  **$t_{max}$**  = time to reach maximum plasma concentration;  **$t_{1/2}$**  = elimination half-life.

**Table II.** Summary of key drug interactions involving oral agents for pulmonary arterial hypertension

Drug/drug group	Tadalafil <sup>[25]</sup>	Sildenafil <sup>[26]</sup>	Ambrisentan <sup>[16]</sup>	Bosentan <sup>[27]</sup>
$\alpha$ -Adrenoceptor antagonists ( $\alpha$ -blockers) and antihypertensives <sup>a</sup>	✓	✓		
Cimetidine		✓		
Cyclosporin (cyclosporine)			✓	✓
Erythromycin		✓		
Glibenclamide (glyburide)				✓
HIV protease inhibitors	✓	✓	✓	✓
Hormonal contraceptives				✓
Ketoconazole/itraconazole	✓	✓		✓
Organic nitrate	✓	✓		
Rifampicin (rifampin)	✓			✓
Simvastatin and other HMG-CoA reductase inhibitors (statins) <sup>b</sup>				✓
Tacrolimus				✓
Vitamin K antagonists/warfarin		✓		✓

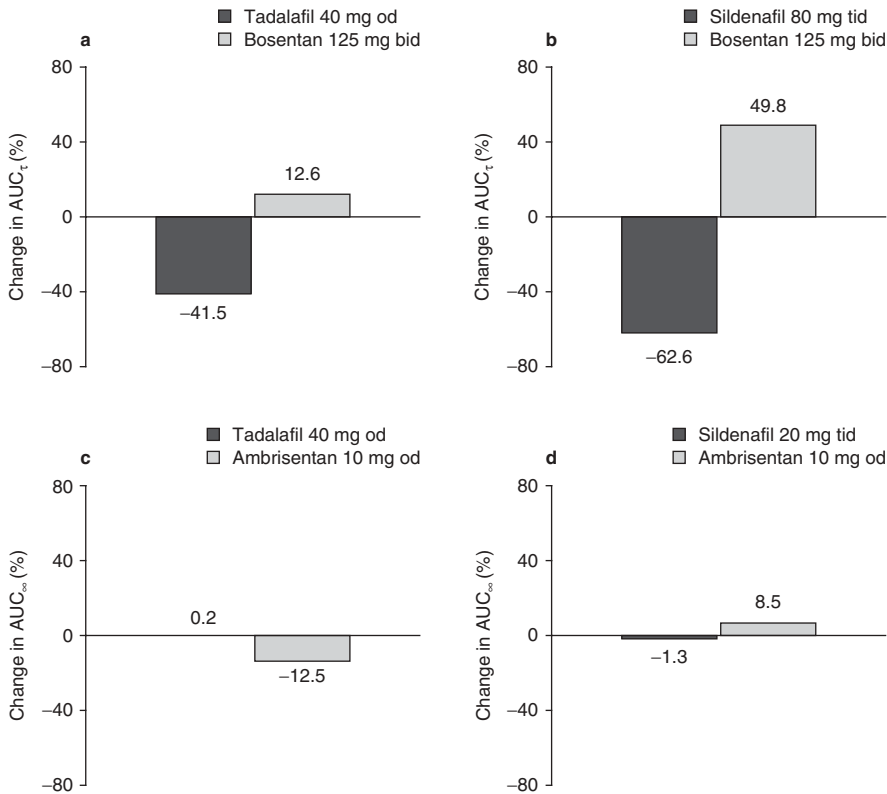
a Amlodipine, angiotensin II type 1 receptor antagonists, bendrofluzide, enalapril and metoprolol.

b Lovastatin and atorvastatin.

CYP3A4 such as rifampicin (rifampin). Bosentan is predominantly metabolized by another isoenzyme, CYP2C9, but is also a potent inducer of CYP3A4. Co-administration of bosentan with warfarin resulted in a decrease in both enantiomers of warfarin (S-warfarin, a CYP2C9 substrate, and R-warfarin, a CYP3A4 substrate).<sup>[28]</sup> In addition, bosentan has significant pharmacokinetic interactions with contraceptives, glibenclamide (glyburide), cyclosporin (cyclosporine) and simvastatin.<sup>[27]</sup> In contrast, there are no known interactions between ambrisentan and warfarin.<sup>[8]</sup> Although not many drug interaction studies have been completed for ambrisentan, this agent appears to have fewer and less significant drug interactions than bosentan, and this may be because ambrisentan is primarily metabolized by glucuronidation and to a lesser extent by CYP3A4.<sup>[29]</sup> Both tadalafil and sildenafil are predominantly metabolized by CYP3A4; however, sildenafil is also metabolized to a lesser extent by CYP2C9.<sup>[23,25]</sup> Specific to the PDE-5 inhibitors, concomitant use of organic nitrate in any form is contraindicated since both sildenafil and tadalafil potentiate the hypotensive effects of nitrates.<sup>[30]</sup> Additionally, sildenafil and tadalafil have been shown to potentiate the hypotensive effect of  $\beta$ -adrenoceptor antagonists ( $\beta$ -blockers).<sup>[23]</sup>

### 2.3 Drug-Drug Interactions with Combination Therapy

The potential for drug-drug interactions through common metabolic pathways of individual therapies must be considered when utilizing combinations of ERAs and PDE-5 inhibitors in the treatment of PAH. Pharmacokinetic studies evaluating the effect of co-administration of these oral agents were conducted in healthy subjects.<sup>[31-34]</sup> Because bosentan is a potent inducer of CYP3A4, co-administration decreased plasma concentrations of sildenafil (area under the plasma concentration-time curve during a dosage interval [AUC<sub>τ</sub>] decreased by 63%) in a study of combination treatment (bosentan 125 mg bid and sildenafil 80 mg tid; figure 1).<sup>[31]</sup> Conversely, sildenafil increased the systemic concentrations of bosentan (AUC<sub>τ</sub> increased by 50%) in this study. In contrast, tadalafil (40 mg od) did not alter bosentan (125 mg bid) concentrations upon co-administration in a separate study, although bosentan decreased tadalafil exposure (AUC<sub>τ</sub>) by 42%.<sup>[32]</sup> Combination of ambrisentan (10 mg od) with either sildenafil (20 mg tid) or tadalafil (40 mg od) demonstrated no clinically relevant pharmacokinetic interactions in separate studies, indicating that no dosage adjustments are required when these agents



**Fig. 1.** Pharmacokinetics of combination oral therapy for pulmonary arterial hypertension. Percentage change in area under the plasma concentration-time curve (AUC) with pharmacokinetic interactions between (a) tadalafil and bosentan;<sup>[32]</sup> (b) sildenafil and bosentan;<sup>[31]</sup> (c) tadalafil and ambrisentan;<sup>[34]</sup> and (d) sildenafil and ambrisentan.<sup>[33]</sup> **AUC<sub>T</sub>** = AUC during a dosage interval; **AUC<sub>∞</sub>** = AUC from time zero to infinity; **bid** = twice daily; **od** = once daily; **tid** = three times daily.

are used in combination.<sup>[33,34]</sup> The significance of these interactions in patients with PAH remains unclear.

### 3. Comparative Efficacy of Oral PAH Therapies

The efficacy of the four oral agents for PAH is summarized in this section by evaluating results from the initial large, double-blind, placebo-controlled, multicentre trials for these agents (tadalafil: PHIRST-1;<sup>[35]</sup> sildenafil: SUPER-1;<sup>[36]</sup> ambrisentan: ARIES-1 and -2;<sup>[37]</sup> and bosentan: BREATHE-1)<sup>[38]</sup> [see table III for full trial names for trial acronyms used in this article]. Drug doses that are approved in the US (i.e. tadalafil 40 mg od, sildenafil 20 mg tid, ambrisentan 5 and 10 mg

od and bosentan 125 mg bid) are evaluated here. All trials were monotherapy trials with the exception of the PHIRST-1 trial<sup>[35]</sup> in which 53% of patients were receiving background bosentan therapy at the time they were randomized to tadalafil or placebo. The primary outcome measured in these trials was change from baseline to end of the trial in exercise capacity as measured by 6-minute walk distance (6MWD). The secondary outcomes included change in WHO FC (similar to NYHA FC), time to clinical worsening (TCW), score on the Borg scale of dyspnoea, hospitalization due to PAH, and quality of life. Safety was assessed on the basis of recorded adverse events. The PHIRST-1<sup>[35]</sup> and BREATHE-1<sup>[38]</sup> studies were 16-week trials, while the SUPER-1 trial<sup>[36]</sup> and ARIES-1 and -2 trials<sup>[37]</sup> were conducted for 12 weeks.

### 3.1 Baseline Characteristics

Although no large, prospective, head-to-head studies of any of the four oral PAH agents have been conducted, baseline characteristics of patients enrolled in these trials were remarkably similar, thus allowing for some level of comparison.<sup>[35-38]</sup> Inclusion of patients in these trials was limited by a 6MWD upper limit of 450 m, even in WHO FC II patients. In each trial, idiopathic PAH (58–77%) was more common than associated PAH. The predominant WHO FCs at baseline among the trials were FC II (30–44%) and FC III (52–65%), except in the BREATHE-1 trial,<sup>[38]</sup> in which all patients belonged to FC III (92%) or FC IV (8%). Although baseline FC data suggest that patients enrolled in the BREATHE-1 trial may have been more sick than patients in the other trials, the baseline haemodynamic parameters (mean pulmonary arterial pressure [mPAP], 53 mmHg; mean cardiac index [CI], 2.5 L/min/m<sup>2</sup>; and mean 6MWD, 326 m) in this trial did not

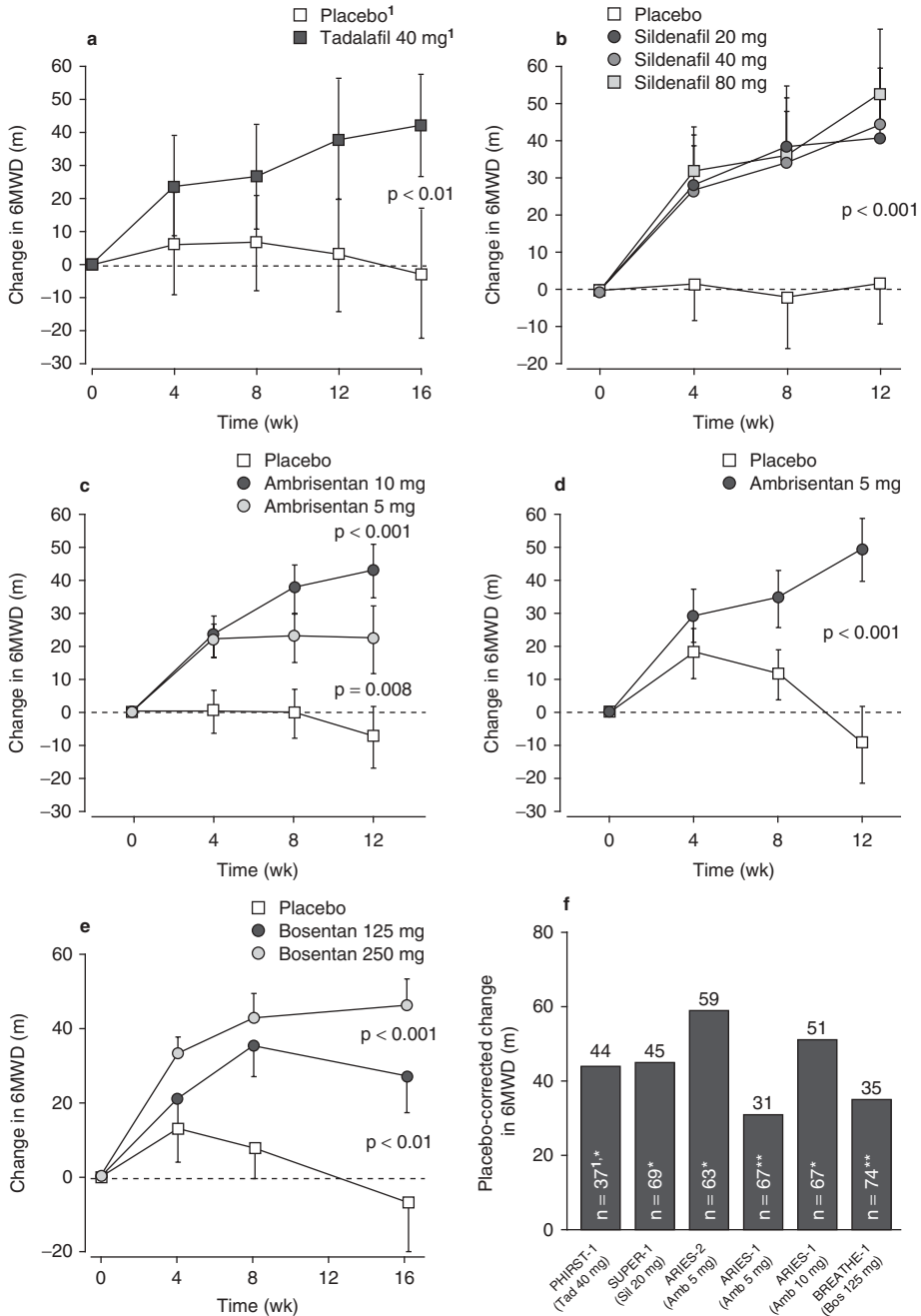
confirm a substantial difference in comparison with the values in the other trials (mPAP, 47–54 mmHg; mean CI, 2.4–2.6 L/min/m<sup>2</sup>; and mean 6MWD, 340–355 m). Since FC assessment can vary among patients and care providers, it may not always correlate with other indices of disease severity.

### 3.2 Six-Minute Walk Distance

At the end of each trial, the mean 6MWDs associated with all doses of the agents included in this evaluation were significantly greater than with placebo ( $p < 0.01$ ) [figure 2].<sup>[35-39]</sup> The mean placebo-corrected 6MWDs were similar across trials, with a range of 31–59 m (figure 2).<sup>[35-39]</sup> It is unclear why the 6MWDs in the 5 mg/day groups varied between the ARIES-1 and ARIES-2 trials (59 m for ARIES-2 vs 31 m for ARIES-1),<sup>[37]</sup> but this difference is within the range of variability reported for other trials. In the PHIRST-1 trial,<sup>[35,39]</sup> the mean placebo-corrected 6MWD was 33 m for the tadalafil 40 mg/day treatment group; however, further subanalysis based on concomitant bosentan therapy demonstrated a change of 44 m in mean placebo-corrected 6MWD in treatment-naïve patients ( $p < 0.01$ ) compared with 23 m for patients receiving background bosentan ( $p =$  not significant). This difference in treatment effect between treatment-naïve patients and patients receiving background bosentan may be a function of smaller patient numbers in the 40 mg/day group or may be related to a ceiling phenomenon that limits additional improvements in disease severity in patients receiving background therapy with targeted PAH medications.<sup>[40]</sup> Indeed, the magnitude of improvement was comparable to that seen in other studies using add-on therapy.<sup>[41,42]</sup> Another explanation may be related to a pharmacokinetic interaction between tadalafil and bosentan mediated by CYP3A4, resulting in reduced tadalafil plasma concentrations. A pharmacokinetic interaction study conducted in healthy subjects suggested that co-administration of bosentan with tadalafil decreased the plasma tadalafil concentration by 42%.<sup>[32]</sup> However, no dose adjustment is recommended and the clinical significance of these interactions is currently unknown.

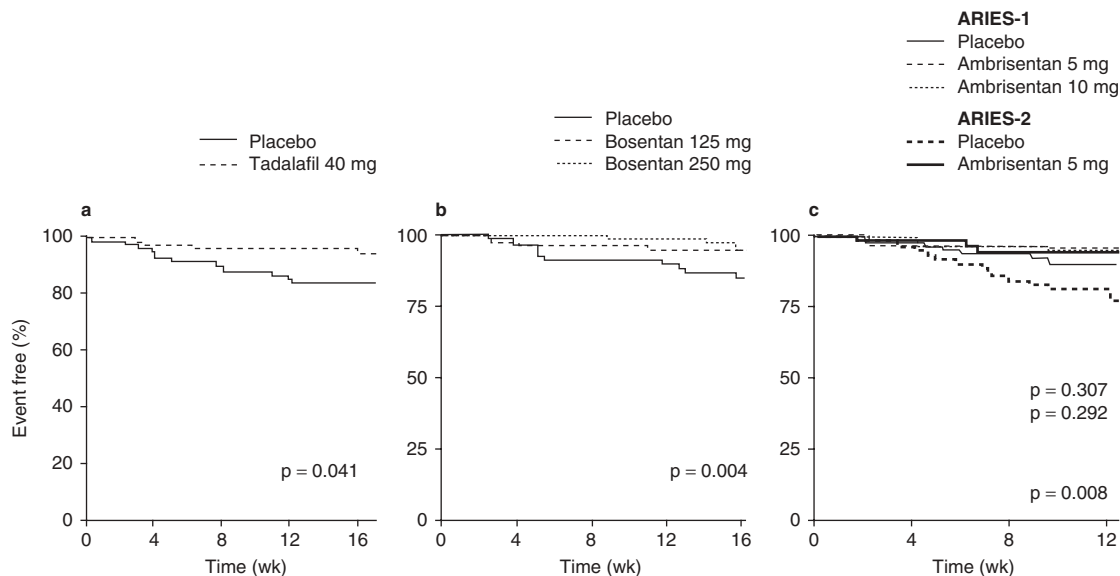
**Table III.** Trial names

ARIES-1, -2 and -E	Ambrisentan in Pulmonary Arterial Hypertension Studies
BREATHE-1 and -2	Bosentan Randomized Trial of Endothelin Antagonist Therapy
COMBI	Combination Therapy of Bosentan and Aerosolised Iloprost in Idiopathic Pulmonary Arterial Hypertension
COMPASS-1 and -2	Effects of Combination of Bosentan and Sildenafil versus Sildenafil Monotherapy on Morbidity and Mortality in Symptomatic Patients with Pulmonary Arterial Hypertension
EARLY	Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients
PACES	Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil
PHIRST-1	Pulmonary Arterial Hypertension and Response to Tadalafil
SERAPH	Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension
STEP	Safety and Pilot Efficacy Trial in Combination With Bosentan for Evaluation in Pulmonary Arterial Hypertension
SUPER-1	Sildenafil Use in Pulmonary Arterial Hypertension



**Fig. 2.** Mean change in 6-minute walk distance (6MWD) from baseline to end of the trial. **(a)** PHIRST-1 trial;<sup>[35,39]</sup> **(b)** SUPER-1 trial (figure adapted with permission from Galie et al.<sup>[36]</sup> Copyright © 2005 Massachusetts Medical Society. All rights reserved) [p-value applies to all three doses of sildenafil vs placebo]; **(c)** ARIES-1 trial (figure adapted with permission from Galie et al.<sup>[37]</sup>); **(d)** ARIES-2 trial (figure adapted with permission from Galie et al.<sup>[37]</sup>); **(e)** BREATHE-1 trial (figure adapted with permission from Rubin et al.<sup>[38]</sup>); **(f)** summary for all trials. **Amb** = ambrisentan; **Bos** = bosentan; **Sil** = sildenafil; **Tad** = tadalafil. **1** Treatment-naive patient subgroup; \* p < 0.001; \*\* p < 0.01 vs placebo. Bars in figures a and b represent 95% confidence intervals. Bars in figures c, d and e represent standard error.





**Fig. 3.** Kaplan-Meier estimates of proportion of patients with clinical worsening. (a) PHIRST-1 (figure adapted with permission from Galie et al.<sup>[36]</sup>); (b) BREATHE-1 (figure adapted with permission from Rubin et al.<sup>[38]</sup> Copyright © 2002 Massachusetts Medical Society. All rights reserved); and (c) ARIES-1 and ARIES-2 (figure adapted with permission from Galie et al.<sup>[37]</sup>). The p-values are reported for comparisons between the study drug and placebo. For the BREATHE-1 trial (figure b), the p-value is reported for the comparison between both doses of bosentan treatment (125 mg and 250 mg combined) vs placebo. For the ARIES-1 and ARIES-2 trials (figure c), the p-values shown are for ARIES-1 ambrisentan 5 mg vs placebo (highest), ARIES-1 ambrisentan 10 mg vs placebo (middle) and ARIES-2 ambrisentan 5 mg vs placebo (lowest).

### 3.3 WHO Functional Class

In the SUPER-1 trial, sildenafil 20 mg tid was associated with significant improvement from baseline in WHO FC ( $p < 0.01$  vs placebo).<sup>[36]</sup> Likewise, the distribution of WHO FC was significantly improved from baseline after ambrisentan treatment in the ARIES-1 trial ( $p = 0.036$  vs placebo).<sup>[37]</sup> However, in the ARIES-2,<sup>[37]</sup> BREATHE-1<sup>[38]</sup> and PHIRST-1<sup>[35]</sup> trials, no statistically significant differences in FC distribution versus placebo were observed. Similar to the effect on exercise capacity, further subanalysis of PHIRST-1 trial<sup>[35]</sup> WHO FC results based on background bosentan use demonstrated that in the treatment-naïve patients, 38% improved and 11% worsened in the tadalafil 40 mg group versus 16% who improved and 22% who worsened in the placebo group ( $p = 0.03$ ).<sup>[12]</sup>

### 3.4 Time to Clinical Worsening

TCW is another clinically important measure of efficacy of PAH medications and may be used

as a possible primary endpoint in future PAH clinical trials (figure 3; table IV).<sup>[35-38]</sup> Statistically significant improvement in TCW or incidence of clinical worsening was observed for patients receiving the investigational agent versus placebo in the PHIRST-1,<sup>[35]</sup> ARIES-2<sup>[37]</sup> and BREATHE-1<sup>[38]</sup> trials. In contrast, this endpoint was not significantly different from placebo in the SUPER-1<sup>[36]</sup> and ARIES-1<sup>[37]</sup> studies. The differences in the TCW measured among these oral agents may be due to variations in how clinical worsening was defined in these trials or how data were imputed.<sup>[35-38]</sup> There were some common components of clinical worsening among these trials: death, hospitalization for PAH, use of other PAH therapy, and lung transplantation. However, components such as worsening WHO FC, discontinuation caused by lack of clinical improvement or worsening of PAH, and early escape (defined as presence of  $\geq 2$  predefined criteria: [i] a decrease of at least 20% in 6MWD; [ii] an increase in  $\geq 1$  WHO FC; [iii] worsening right ventricular failure; [iv] rapidly progressing hepatic or renal

**Table IV.** Summary of clinical worsening from oral agents for pulmonary arterial hypertension (PAH)

Variable	PHIRST-1 <sup>[35]</sup>		SUPER-1 <sup>[38]</sup>		ARIES-1 <sup>[37]</sup>		ARIES-2 <sup>[37]</sup>		BREATHE-1 <sup>[38]</sup>		
	placebo (n=82)	tadalafil 40 mg od (n=79)	placebo (n=70)	sildenafil 20 mg tid (n=69)	placebo (n=67)	ambrisentan 5 mg od (n=67)	ambrisentan 10 mg od (n=67)	placebo (n=64)	ambrisentan 5 mg od (n=63)	placebo (n=68)	bosentan 125 mg bid (n=74)
Clinical worsening (%) <sup>a</sup>	16	5 <sup>b</sup>	10	4 <sup>c</sup>	9	4 <sup>c</sup>	4 <sup>c</sup>	22	5 <sup>b</sup>	20	7 <sup>b</sup>
death	1	0	1	1	3	1	1	5	0	3	1
hospitalization for PAH	2	1	10	3	3	3	3	14	3	13	4
worsening WHO FC	13	4	NA	NA	NA	NA	NA	NA	NA	NA	NA
other PAH therapy	0	1	1	0	1	0	1	0	0	4	3
discontinuation <sup>d</sup>	NA	NA	NA	NA	NA	NA	NA	NA	NA	9	4
early escape <sup>e</sup>	NA	NA	NA	NA	6	0	3	11	2	NA	NA

a More than one event occurred in some patients.

b p < 0.05 vs placebo.

c Not statistically significant vs placebo.

d Because of lack of clinical improvement or worsening of PAH.

e Defined as the presence of two or more of the following criteria: (i) decrease of  $\geq 20\%$  in 6-minute walk distance; (ii) increase of  $\geq 1$  WHO FC; (iii) worsening right ventricular failure; (iv) rapidly progressing hepatic or renal failure; and (v) refractory systolic hypotension.

**bid** = twice daily; **NA** = not applicable; **od** = once daily; **tid** = three times daily; **WHO FC** = World Health Organization functional class.

failure; and [v] refractory systolic hypotension), were used only in the PHIRST-1,<sup>[35]</sup> BREATHE-1,<sup>[38]</sup> and ARIES-1 and ARIES-2<sup>[37]</sup> trials, respectively. Indeed, the significance of differences in TCW appears to be driven by the relative rate of deterioration in the placebo arms of these trials, and some trials may not be of sufficient duration for patients to deteriorate according to the current definitions.

### 3.5 Haemodynamics

A change in haemodynamics was another secondary endpoint measured in the PHIRST-1<sup>[35,39]</sup> and SUPER-1<sup>[36]</sup> trials. Improvements from baseline in mPAP, mean PVR and mean CI were observed in patients receiving tadalafil or sildenafil in these trials (table V).<sup>[35,36,39]</sup> Although haemodynamics were not assessed in the BREATHE-1 trial,<sup>[38]</sup> another bosentan trial (EARLY) demonstrated haemodynamic benefits with this oral agent.<sup>[43]</sup>

### 3.6 Quality of Life

Quality of life represents another important endpoint, although no oral PAH therapy trial has utilized a validated disease-specific assessment of this outcome. Improvement in quality-of-life indices was reported in the ARIES-2<sup>[37]</sup> and PHIRST-1<sup>[35]</sup> trials. The Short Form-36 (SF-36) Health Survey physical functioning score significantly improved in the combined ambrisentan (2.5 mg and 5 mg) group in the ARIES-2 trial compared with the placebo group.<sup>[37]</sup> In contrast to the ARIES-2 trial, no quality-of-life endpoints were significantly different among the ambrisentan 5 mg and 10 mg and placebo groups in the ARIES-1 trial.<sup>[37]</sup> Statistically significant improvements from baseline to week 16 compared with placebo were observed in six of the eight domains in the SF-36 Health Survey for the tadalafil 40 mg group in the PHIRST-1 trial.<sup>[35]</sup> The quality-of-life improvements observed in the PHIRST-1 trial are particularly interesting since some of the patients who experienced these improvements were already receiving background bosentan treatment, suggesting for the first time that add-on therapy can lead to further improvements in quality of life for patients with PAH.

**Table V.** Haemodynamic responses to tadalafil and sildenafil<sup>a</sup>

Parameter	PHIRST-1 <sup>[35]</sup>			SUPER-1 <sup>[36]</sup>		
	placebo (n=16)	tadalafil 40 mg od (n=18)	p-value	placebo (n=65)	sildenafil 20 mg tid (n=65)	p-value
Heart rate (beats/min)	-2.1	2.6	NS	-1.3	-3.7	NS
mPAP (mmHg)	-2.2	-4.3	0.01	0.6	-2.1	0.04
RAP (mmHg)	-0.8	-1.2	NS	0.3	-0.8	NS
CI (L/min/m <sup>2</sup> )	-0.01 <sup>b</sup>	0.4 <sup>b</sup>	0.01 <sup>b</sup>	-0.02	0.2	NS <sup>c</sup>
PVR (dyn • s • cm <sup>-5</sup> )	11.0	-209.2	0.04	49	-122.0	0.01

a Data are mean changes from baseline.

b Data on file.<sup>[39]</sup>

c Statistical significance was met for 240 mg/day regimen in this trial (p=0.001).

CI=cardiac index; mPAP=mean pulmonary arterial pressure; NS=not significant; od=once daily; PVR=pulmonary vascular resistance; RAP=right atrial pressure; tid=three times daily.

### 3.7 Survival with Long-Term Therapy

Survival with long-term treatment has been studied for bosentan, ambrisentan and sildenafil.<sup>[2]</sup> Favourable survival for a 3-year period with first-line bosentan treatment was demonstrated in patients from two placebo-controlled clinical trials<sup>[38,44]</sup> who continued treatment with open-label bosentan during the trial extension periods (96%, 89% and 86% survival at 1, 2 and 3 years, respectively).<sup>[45]</sup> These data were validated in a real-life, retrospective study with a mean follow-up of 24 months, which reported similar improvements in exercise capacity and haemodynamics, indicative of continued efficacy of bosentan in the treatment of PAH.<sup>[46]</sup> Patients from the ARIES-1 and ARIES-2 trials<sup>[37]</sup> continued treatment with ambrisentan in the long-term ARIES-E study.<sup>[47]</sup> The probability of survival of patients who received placebo in ARIES-1 or ARIES-2 and ambrisentan in ARIES-E (93%) or ambrisentan in ARIES-1 or ARIES-2 and in ARIES-E (94%) was similar in these two treatment groups. The Kaplan-Meier estimate of 3-year survival from an open-label study of sildenafil with highest tolerable dose (20, 40 or 80 mg tid) was 79%, and 61% of patients had unchanged or improved functional status.<sup>[48]</sup> It should be noted that the majority of the patients (82%) in this long-term study received sildenafil 80 mg tid, while the sildenafil dose approved by the US FDA for the treatment of PAH is 20 mg tid. Therefore, in

clinical practice, up-titration of the sildenafil dose to 80 mg tid may be needed to maintain long-term efficacy. In contrast, it is unknown whether a similar up-titration of dose will be needed for tadalafil treatment over time. Tadalafil is currently being investigated in an open-label extension trial; at a mean follow-up of 44 weeks in this study, there were 4.6 deaths per 100 patient-years.<sup>[49]</sup>

The efficacy data for the oral therapies for PAH suggest that the effects observed with respect to 6MWD, TCW and haemodynamic properties are not heterogeneous among the different classes of drugs. This lack of heterogeneity in efficacy of ERAs and PDE-5 inhibitors is exemplified in a randomized, multiple-dose, 16-week trial (SERAPH) comparing sildenafil (50 mg bid for 4 weeks, then 50 mg tid) with bosentan (62.5 mg bid for 4 weeks, then 125 mg bid).<sup>[50]</sup> There was no significant difference between patients treated with sildenafil (n=14) and bosentan (n=12) regarding right ventricular mass, 6MWD, CI, Borg dyspnoea score or quality-of-life endpoints. These results, along with those observed in the large randomized trials, may suggest that other properties and features of these agents, such as safety and convenience, are also important in treatment decisions.

### 4. Comparative Tolerability of Oral PAH Therapies

Common adverse events for the four targeted oral therapies for PAH are summarized in tables VI

and VII.<sup>[35-38]</sup> The most common adverse events noted in clinical trials included headache and dizziness for bosentan and peripheral oedema, headache and nasal congestion for ambrisentan. Indeed, peripheral oedema appears to be a class effect that warrants close monitoring of the dose of diuretic and heart function. Common adverse events with PDE-5 inhibitors in the treatment of PAH reported in the SUPER-1<sup>[36]</sup> and PHIRST-1<sup>[35]</sup> trials included headache, myalgia, flushing, diarrhoea, back pain and dyspepsia.

The main adverse event of interest for the ERA agents is hepatocellular injury. In clinical studies, bosentan treatment led to approximately 11% of patients experiencing a >3-fold increase in hepatic transaminase levels compared with normal levels.<sup>[14]</sup> Because of this adverse event, monthly monitoring of liver function is mandated, and patients with baseline liver dysfunction should not receive the drug. Although the transaminase levels return to pretreatment levels within a few days to 9 weeks after discontinuing the drug, there are concerns about the potential for severe and permanent liver damage.<sup>[51]</sup> A postmarketing surveillance study confirmed that the incidence and severity of increased transaminase levels in patients treated with bosentan in clinical practice was similar to that reported in clinical trials.<sup>[51]</sup> Like bosentan,

ambrisentan also carries a black box warning for potential liver injury requiring monthly monitoring of liver function tests. However, in contrast to bosentan, the risk of liver injury with ambrisentan appears to be much lower. In a phase II study of 64 patients with PAH treated with ambrisentan, the incidence of hepatic transaminase elevation >3-fold the normal levels was 3%.<sup>[52]</sup> However, in the ARIES-1 and ARIES-2 trials, no patient developed elevated transaminase levels >3-fold the normal levels.<sup>[37]</sup>

Both bosentan and ambrisentan are also contraindicated in pregnancy due to teratogenicity (FDA pregnancy category X). Since ERAs are potent teratogens,<sup>[53]</sup> proof of contraception is required for women of child-bearing potential before starting treatment. Due to the drug interaction of bosentan with hormonal contraceptives, the possibility of contraceptive failure exists, necessitating the use of a second form of birth control.

Because of the contraindications to their use, distribution of bosentan and ambrisentan is restricted under programmes aimed at minimizing liver injury and birth defects associated with these drugs (bosentan: Tracleer Access Program; ambrisentan: Letairis Education and Access Program). Consequently, the ERA class of drugs is distributed through specialty pharmacies.

Peripheral oedema has been reported to be an ERA group-specific adverse effect. Therefore, a warning label has been issued by the FDA for ambrisentan based on post-marketing reports of fluid retention occurring within weeks after starting the drug.<sup>[16]</sup>

The use of organic nitrates (such as nitroglycerin) is contraindicated with PDE-5 inhibitor administration, as the combination potentiates hypotensive effects. This is especially pertinent in patients with mixed heart disease or coronary artery disease. In some cases, sildenafil use has been associated with visual disturbances owing to PDE-6 inhibition in the retina. In the SUPER-1 trial, the incidence of visual disturbance was 4% and 7% of patients treated with sildenafil 40 mg and 80 mg tid, respectively.<sup>[36]</sup> The increased incidence of myalgia reported with tadalafil (PHIRST-1)<sup>[35]</sup> as compared with sildenafil (SUPER-1)<sup>[36]</sup> may be due to the greater effect of

**Table VI.** Adverse events (%) associated with oral phosphodiesterase 5 inhibitors for pulmonary arterial hypertension<sup>a</sup>

Adverse event	PHIRST-1 <sup>[35]</sup>		SUPER-1 <sup>[36]</sup>	
	placebo (n=82)	tadalafil 40 mg od (n=79)	placebo (n=70)	sildenafil 20 mg tid (n=69)
Headache	15	42	39	46
Myalgia	4	14	4	7
Back pain	6	10	11	13
Flushing	2	13	4	10
Dyspepsia	2	10	7	13
Diarrhoea	10	11	6	9
Nausea	6	11		
Pain in extremity	2	11		

<sup>a</sup> Adverse events listed here are those reported by ≥10% of patients in any one of the treatment groups.

**od**=once daily; **tid**=three times daily.

**Table VII.** Adverse events (%) associated with oral endothelin receptor antagonists for pulmonary arterial hypertension<sup>a</sup>

Adverse event	ARIES-1 <sup>[37]</sup>			ARIES-2 <sup>[37]</sup>		BREATHE-1 <sup>[38]</sup>	
	placebo (n=67)	ambrisentan 5 mg od (n=67)	ambrisentan 10 mg od (n=67)	placebo (n=65)	ambrisentan 5 mg od (n=63)	placebo (n=69)	bosentan 125 mg bid (n=74)
Peripheral oedema	10	27	28	11	10		
Headache	21	18	19	6	13	19	19
Dizziness						19	12
Cough						12	5
Nasal congestion	3	6	10	0	5		
Syncope						6	8
Abnormal hepatic function						3	4

a Adverse events listed here are those reported by  $\geq 10\%$  of patients in any one of the treatment groups in the trial.

**bid** = twice daily; **od** = once daily.

tadalafil on PDE-11A (the predominant PDE in skeletal muscle). Surprisingly, the incidence of back pain was similar in sildenafil-treated patients in the SUPER-1 trial<sup>[36]</sup> and tadalafil-treated patients in the PHIRST-1 trial.<sup>[35]</sup>

Taken together, the safety and tolerability of oral agents in the treatment of PAH demonstrate that the PDE-5 inhibitor class appears to have a more favourable safety profile than the ERA class. Unlike the ERAs, access to PDE-5 inhibitors is not restricted, and these drugs are distributed through traditional retail pharmacies. However, more ready access to PDE-5 inhibitors may lead to inappropriate prescription. Indeed, it is likely that some patients are treated with PDE-5 inhibitors in the absence of right heart catheterization-confirmed diagnosis of PAH. Therefore, to help ensure that only patients with PAH are treated with oral therapy, diagnosis of PAH should always entail right heart catheterization.

## 5. Oral Combination-Based Regimens

Because the disease pathways in PAH are unique but interrelated, targeting more than one pathway may have an additive or synergistic effect on efficacy in treating patients. However, safety and tolerability issues associated with combination treatments should be carefully considered since potential drug interactions can make their use in combination unfavourable, particularly if used 'up-front' in combination. It also may be un-

clear which drug is causing adverse effects when two are used together in first-line therapy. Data on oral-based combination therapies obtained thus far have been mostly derived from small studies. The combination of sildenafil and bosentan was evaluated in a study (COMPASS-1) of 45 patients with PAH who had been taking bosentan therapy for at least 12 weeks.<sup>[54]</sup> A single oral dose of sildenafil (25 mg) reduced mean PVR by 15% from baseline to 60 minutes after administration. Another placebo-controlled trial evaluating the combination of bosentan and sildenafil for 16 weeks is ongoing and includes 6MWD, death, lung transplantation, atrial septostomy, hospitalizations and need for more aggressive therapies as endpoints.<sup>[55]</sup>

The effect of adding ERA to prostacyclin therapy was evaluated in the randomized, double-blind, placebo-controlled BREATHE-2 study.<sup>[56]</sup> Patients with severe PAH (n=33; NYHA FC III and IV) were started on epoprostenol for 2 days and randomized to receive add-on bosentan (n=22) or placebo (n=11) for the next 16 weeks. Epoprostenol was initiated at a dose of 2 ng/kg/min and was up-titrated to  $14 \pm 2$  ng/kg/min at week 16; bosentan was started at 62.5 mg bid for 4 weeks and then up-titrated to 125 mg bid. There were improvements in haemodynamics in the combination treatment group, but these were not statistically significant compared with epoprostenol plus placebo. Results from two trials that studied the combination of bosentan with an inhaled prostanoid, iloprost, have been mixed. A small 12-week

study (STEP) of 67 patients with PAH demonstrated a mean 26 m improvement in 6MWD versus placebo in patients treated with bosentan who were randomized to receive iloprost.<sup>[41]</sup> However, another 12-week study (COMBI) of 40 patients failed to show a positive effect of adding inhaled iloprost to bosentan in patients with idiopathic PAH.<sup>[57]</sup>

Finally, the combination of PDE-5 inhibitors and prostacyclin therapy was studied in the large (n = 267), randomized, double-blind, placebo-controlled, PACES trial in which patients who were stable on intravenous epoprostenol were randomized to receive placebo (n = 133) or sildenafil (n = 134; initially 20 mg tid then titrated to 40 mg and 80 mg tid as tolerated).<sup>[42]</sup> A placebo-adjusted mean increase of 29 m in 6MWD was demonstrated in patients receiving the combination therapy at the end of 16 weeks, indicating an additive effect of these two drugs. Also by the end of 16 weeks, fewer patients in the sildenafil group versus the placebo group had clinical worsening events.

Many of the combination trials discussed here were evaluated using small patient populations, and these initial experiences are encouraging. Although combination therapies may have potential for improved efficacy, PACES is so far the only study that has demonstrated a clear benefit of combination-based regimens. More combination therapies are currently being studied in large, well designed, placebo-controlled clinical trials that may provide more evidence for their use in the treatment of PAH.<sup>[9]</sup>

## 6. Conclusions

An increase in understanding of the molecular mechanisms underlying the pathogenesis of PAH has resulted in the discovery of a number of novel therapies in recent years, providing an ever-increasing number of new treatment options for the PAH community. This is an exciting period for patients and physicians as more oral agents are introduced or are under development for the treatment of PAH. Availability of several oral agents increases both patients' and physicians' options and exemplifies the rapid progress in the field in the last 15–20 years. All agents have re-

lative advantages and disadvantages, which may make one agent or the other more useful as first-line therapy, add-on therapy or use up-front in novel combination regimens. Combination therapy using drugs with different mechanisms of action may be an appealing option for patients who do not respond adequately to monotherapy. Drugs associated with a lower incidence of adverse events and decreased risk of drug interactions, such as tadalafil and ambrisentan, are attractive candidates for combination therapy. Given the increased treatment options available for PAH, physicians will be able to consider factors such as dosing, convenience/adherence, safety, drug interactions, quality of life, and suitability for use in combination regimens when treating patients with PAH.

## Acknowledgements

Editorial assistance was provided under the direction of the author by MedThink Communications, Inc., with support from United Therapeutics Corporation. Dr Safdar has received consultancy fees and honoraria from United Therapeutics, Actelion Pharmaceuticals Ltd, and Gilead Sciences, Inc., and has stock ownership options of less than \$US5000.00 for Gilead Sciences, Encysive Pharmaceuticals Inc., and United Therapeutics. Dr Safdar did not receive any funding for the preparation of this review article. The decision to submit this manuscript to *Clinical Drug Investigation* was made by Dr Safdar.

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