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The Pharmacological Treatment of Pulmonary Arterial Hypertension

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Abstract—Pulmonary arterial hypertension (PAH) is a life-threatening and progressive disease of various origins characterized by pulmonary vascular remodeling that leads to increased pulmonary vascular resistance and pulmonary arterial pressure, most often resulting in right-sided heart failure. The most common symptom at presentation is breathlessness, with impaired exercise capacity as a hallmark of the disease. Advances in understanding the pathobiology over the last 2 decades have led to therapies (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclins or analogs) initially directed at reversing

the pulmonary vasoconstriction and more recently directed toward reversing endothelial cell dysfunction and smooth muscle cell proliferation. Despite these advances, disease progression is common even with use of combination regimens targeting multiple mechanistic pathways. Overall 5-year survival for PAH has increased significantly from approximately 30% in the 1980s to approximately 60% at present, yet remains abysmal. This review summarizes the mechanisms of action, clinical data, and regulatory histories of approved PAH therapies and describes the latest agents in late-stage clinical development.

I. Introduction

Pulmonary arterial hypertension (PAH¹) is a progressive disease characterized by increased pulmonary vas-

cular resistance, leading to chronic elevation in pulmonary arterial pressure resulting from restricted flow through the pulmonary arterial circulation. These pathobiological features typically lead to right-sided

¹Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); AWP, average wholesale price; CI, confidence interval; CML, chronic myelogenous leukemia; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; EMA, European Medicines Agency; EPC, endothelial progenitor cell; ERA, endothelin receptor antagonist; ET, endothelin; EU, European Union; FDA, U.S. Food and Drug Administration; mPAP, mean pulmonary artery pressure; NAION, nonarteritic anterior ischemic

optic neuropathy; NYHA, New York Heart Association; P450, cytochrome P450; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PDGF, platelet-derived growth factor; PDGF-R, platelet-derived growth factor receptor; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; prostacyclin, prostaglandin I₂; PVR, pulmonary vascular resistance; WHO, World Health Organization.

heart failure and premature death (Barst et al., 2004b; Galié et al., 2009b). No large-scale epidemiological studies evaluating the prevalence of PAH have been published, but several registries in the United States and Europe suggest that the prevalence of PAH in adults is approximately 12 to 50 per million people (Humbert et al., 2006; Peacock et al., 2007; Frost et al., 2011). This figure may be an underestimation given continued advances in the diagnosis of the disease. The Registry to EVAluate Early And Long-term pulmonary arterial hypertension (REVEAL) is the largest registry of PAH reported to date, with 2525 U.S. adults meeting traditional hemodynamic criteria; mean age at diagnosis was 50 years with a four-to-one female predominance (Badesch et al., 2010).

The current classification of pulmonary hypertension (PH) has group 1 synonymous with PAH and its subcategories (Table 1) (Simonneau et al., 2009). Idiopathic PAH occurs in the absence of known risk factors and is the most common form of the disease (Galié et al., 2009b; Badesch et al., 2010). Figure 1 shows the distribution of additional subcategories of PAH reported from REVEAL, which includes a familial form (now termed heritable), a form attributable to drugs and toxins, and forms in association with connective tissue diseases, congenital heart diseases, HIV infection, portal hypertension, and other systemic conditions (Badesch et al., 2010).

PAH is a lethal disease. The median period of survival after diagnosis, based on an early U.S. National Institutes of Health Registry with prospective follow-up, was less than 3 years for 194 untreated patients with idiopathic or heritable PAH (formerly called primary pulmonary hypertension) with a mean age of 36 years (Rich et al., 1987; D'Alonzo et al., 1991). At present, average survival after diagnosis in adults is estimated at 5 to 7 years (Gomberg-Maitland et al., 2011; Kane et al., 2011; Benza et al., 2012), with a similarly poor overall prognosis in children (Barst et al., 2011a).

The pathobiology of PAH is poorly understood but includes pathologic changes in the intima, media, and adventitial layers of the vascular wall. Both vascular endothelial and smooth muscle cells have characteristics of abnormal growth, with excess cellular proliferation and apoptosis resistance (Fig. 2). These abnormalities in resident vascular cells, in combination with inflammation, excess vasoconstriction, and in situ thrombosis, contribute to physical narrowing of the distal pulmonary arterioles. This narrowing causes a dramatic increase in pulmonary vascular resistance, which leads to the chronic and progressive elevation of pulmonary arterial pressure. Odd clusters of immature blood vessels with endothelial cell proliferation (called plexiform lesions) are also characteristic pathologic abnormalities in PAH and are not found in diseases of the systemic circulation (Rabinovitch 2007).

TABLE 1

Current clinical classification of pulmonary hypertension from the 4th World Symposium on Pulmonary Hypertension (Dana Point, CA, 2008)

[Reprinted from Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langen D, Nakanishi N, and Souza R (2009) Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 54:S43–S54. Copyright © 2009 Elsevier. Used with permission.]

1. Group 1 pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic PAH
 - 1.2. Heritable
 - 1.2.1. BMPR2
 - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
 - 1.2.3. Unknown
 - 1.3. Drug- and toxin-induced
 - 1.4. Associated with
 - 1.4.1. Connective tissue diseases
 - 1.4.2. HIV infection
 - 1.4.3. Portal hypertension
 - 1.4.4. Congenital heart diseases
 - 1.4.5. Schistosomiasis
 - 1.4.6. Chronic hemolytic anemia
 - 1.5 Persistent pulmonary hypertension of the newborn
- 1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Group 2 pulmonary hypertension owing to left heart disease
 - 2.1. Systolic dysfunction
 - 2.2. Diastolic dysfunction
 - 2.3. Valvular disease
3. Group 3 pulmonary hypertension owing to lung diseases and/or hypoxia
 - 3.1. Chronic obstructive pulmonary disease
 - 3.2. Interstitial lung disease
 - 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
 - 3.4. Sleep-disordered breathing
 - 3.5. Alveolar hypoventilation disorders
 - 3.6. Chronic exposure to high altitude
 - 3.7. Developmental abnormalities
4. Group 4 chronic thromboembolic pulmonary hypertension (CTEPH)
5. Group 5 pulmonary hypertension with unclear multifactorial mechanisms
 - 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
 - 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
 - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
 - 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, activin receptor-like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2.

Therapies for PAH target the prostacyclin, endothelin, or nitric oxide (NO) pathways and are believed to be efficacious by reversing or diminishing vasoconstriction, vascular endothelial cell proliferation, smooth muscle cell proliferation, and endothelial dysfunction (Boutet et al., 2008; McGoon and Kane, 2009). For example, prostacyclins are potent vasodilators that can also inhibit vascular smooth muscle growth. PAH is associated with reduced pulmonary levels of prostacyclin as a result of underexpression of endothelial prostacyclin synthase. Endothelin receptor antagonists (ERAs) block the effect of endothelin, a potent endogenous vasoconstrictor and mitogen, at smooth muscle cell receptors. Phosphodies-

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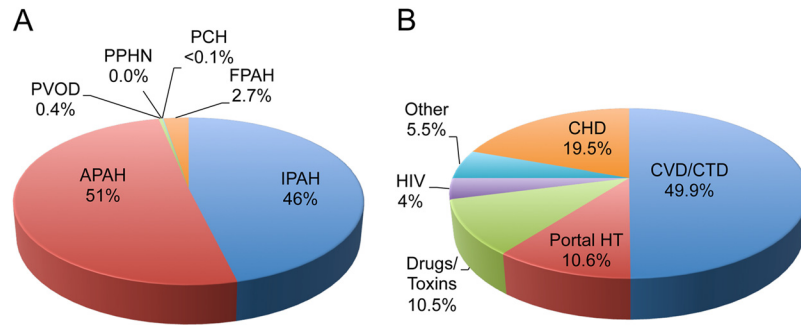


FIG. 1. World Health Organization (WHO) group 1 PAH classification of REVEAL (U.S. Registry) patients at enrollment. A, WHO group 1 classification. B, breakdown of associated PAH (APAH) subgroup. The most current classification revised the category of familial PAH (FPAH) used at the time of the REVEAL registry to heritable PAH to reflect advances in identifying familial cases with and without germline mutations (Simonneau et al., 2009) (Table 1). CHD, congenital heart disease; CVD/CTD, collagen vascular disease/connective tissue disease; HT, hypertension; IPAH, idiopathic PAH; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary venoocclusive disease. [Reprinted from Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, et al. (2010) Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 137:376–387. Copyright © 2010 American College of Chest Physicians. Used with permission.]

terase type 5 (PDE-5) inhibitors facilitate vasodilation by promoting the activity of the nitric oxide pathway by inhibiting degradation of cGMP, a second messenger that prompts relaxation of vascular smooth muscle. New therapies under development target these and additional pathways.

II. Current Treatment Options

A. History of Product Approvals

Approved drugs currently used in the treatment of PAH in North America or the European Union (EU) include the orally administered PDE-5 inhibitors sildenafil (Revatio) and tadalafil (Adcirca), the dual ERA bosentan (Tracleer), and the selective endothelin-1_A receptor antagonist ambrisentan [Letairis (United States)/Volibris (international)]. Patients with more advanced disease are often treated with prostacyclins or prostacyclin analogs such as iloprost (Ventavis) or treprostinil (Tyvaso) given as multiple daily inhalations, epoprostenol (Flolan/Veletri) or treprostinil (Remodulin) given as continuous intravenous infusions, or treprostinil also used as a continuous subcutaneous infusion. Intravenous injection of sildenafil is approved for patients who are currently prescribed but are temporarily unable to take oral sildenafil. Inhaled nitric oxide (INO_{max}) is approved for the neonatal form of PAH—persistent pulmonary hypertension of the newborn (PPHN).

This section briefly reviews the route of administration, mechanism of action, and approval histories of 8 drugs (including their different formulations) that target the prostacyclin (epoprostenol, iloprost, treprostinil), endothelin (bosentan, ambrisentan), and nitric oxide (tadalafil, sildenafil, NO) pathways and are currently used in the treatment of PAH in North America or the EU (Fig. 3). The drugs are reviewed in more detail in subsequent sections.

1. Epoprostenol. Epoprostenol, which requires continuous infusion through a central venous catheter and infusion pump, is synthetic prostacyclin. The U.S. Food

and Drug Administration (FDA) approved epoprostenol in 1995 for use as a continuous intravenous treatment for patients with World Health Organization (WHO) functional classes III (moderate) and IV (severe) symptoms and for primary pulmonary hypertension that does not respond adequately to conventional therapy. Subsequent label revisions have included the addition of patients with PAH related to scleroderma (2000) and all patients with PAH (PH group 1) regardless of etiology to improve exercise capacity (2011).

Epoprostenol reduces morbidity and improves survival; the latter has been demonstrated mainly in those with idiopathic PAH in a pivotal controlled trial (comparing conventional therapy) and in open-label, observational studies that have also included other subgroups of PAH. Adverse events are primarily related to its continuous intravenous delivery system and include jaw pain, nausea, and diarrhea, with potentially serious, life-threatening complications such as bloodstream infections, sepsis, thromboembolic events, and inadvertent drug interruption. With the availability of other therapies, epoprostenol is most often reserved for patients with advanced symptoms who do not adequately improve on oral or inhaled drugs. It is unusual for a patient to be awaiting transplantation without receiving epoprostenol. Epoprostenol is available in over 20 countries, including the United States, Canada, Japan, Australia, and select regions in Europe. The patent for epoprostenol expired in 2007. In 2008, the FDA approved both the first generic version of epoprostenol and a new intravenous formulation (i.e., Veletri) that is more stable at room temperature.

2. Treprostinil. Treprostinil is a prostacyclin analog administered as a continuous subcutaneous or intravenous infusion (Remodulin) or by inhalation (Tyvaso). The FDA (and Health Canada) approved treprostinil given subcutaneously in 2002 for the relief of symptoms associated with exercise in patients with PAH in New York Heart Association (NYHA) functional classes II to

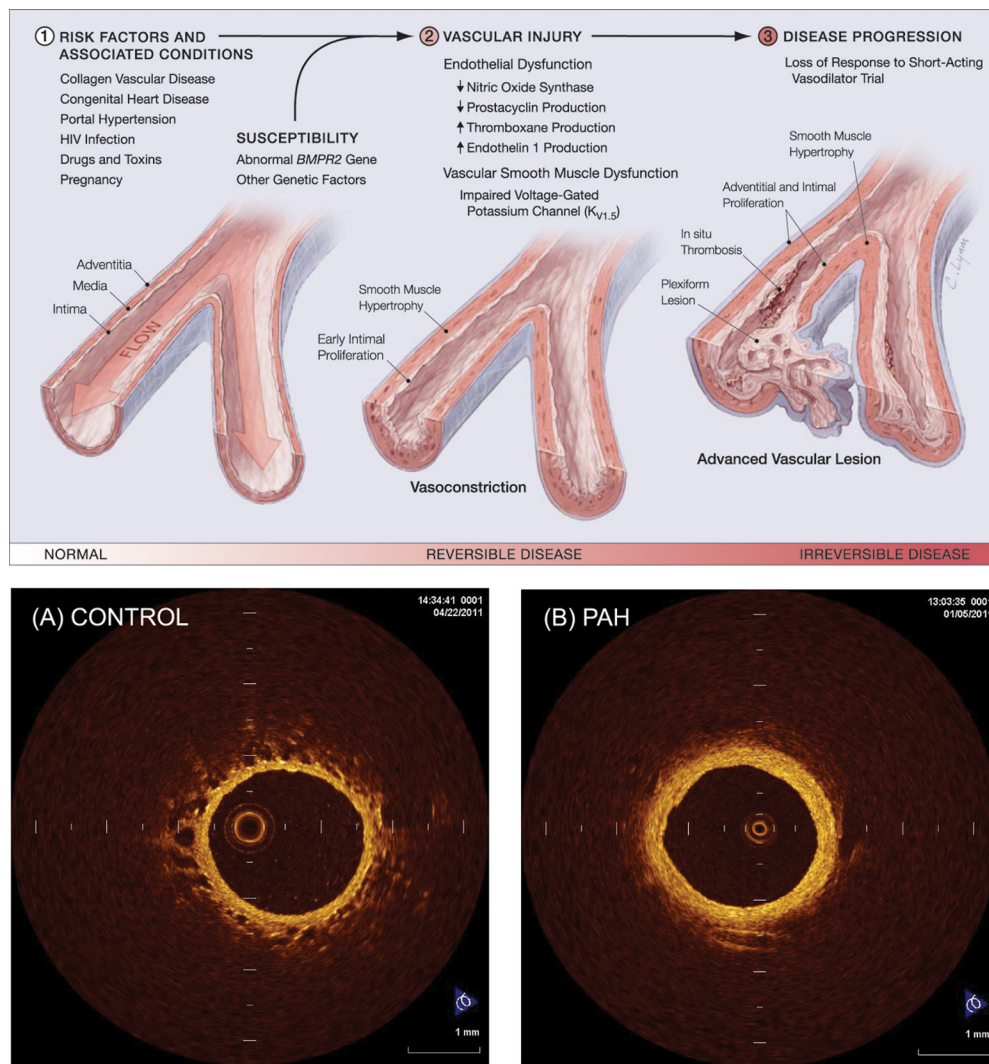


FIG. 2. Characteristic pathological features of PAH. Top, diagram showing progression to vasoconstriction (and related smooth muscle hypertrophy), vascular cell proliferation, and thrombosis in situ. [Reprinted from Gaine S (2000) Pulmonary hypertension. *JAMA* 284:3160–3168. Copyright © 2000 American Medical Association. Used with permission.] Bottom, representative optical coherence tomography images of distal pulmonary arteries with comparable luminal areas for patient with normal pulmonary artery pressure (A) and patient with idiopathic PAH diagnosed 5 years earlier (B), showing vascular intima and media nearly twice the thickness (0.28 versus 0.16 mm). Scale bar, 1.0 mm. Courtesy of Dr. Yoshihiro Fukumoto (Tohoku University, Sendai, Japan).

IV (mild to severe symptoms). Treprostinil was subsequently launched in most of Europe, Canada, and other regions. Infusion site pain and reactions are the most common adverse events with subcutaneous treprostinil; these events are reported in more than 80% of patients but wane over time in many (Galié et al., 2009b). In 2004, on the basis of data establishing bioequivalence, the FDA approved an intravenous formulation of treprostinil for patients with PAH in functional classes II to IV who do not tolerate the subcutaneous form or in whom intravenous administration may be preferable to subcutaneous infusion. In early 2006, the FDA expanded the intravenous Remodulin label to include patients in whom transition from epoprostenol may provide a better overall quality of life because of its temperature stability and longer half-life. In 2009, an inhaled form of treprostinil was approved in the United States to improve

exercise capacity in patients with PAH in functional class III (moderate), with recommended four times daily dosing.

3. Iloprost. Iloprost is a prostacyclin analog initially approved as an aerosolized form in the EU and Australia (in 2003) for patients with idiopathic PAH and functional class III status, and in the United States (in 2004) for patients with PAH and functional class III (moderate) or IV (severe) symptoms. Iloprost was later launched in additional regions. Iloprost is generally well tolerated, although a significant limitation is its short elimination half-life (20–25 min), with recommended dosing of six to nine times daily. The most frequent adverse events are cough, headache, and flushing.

4. Bosentan. Bosentan is a dual-endothelin (ET-1_{A/B}) receptor antagonist that was initially approved by the FDA in 2001 to improve exercise ability and decrease the

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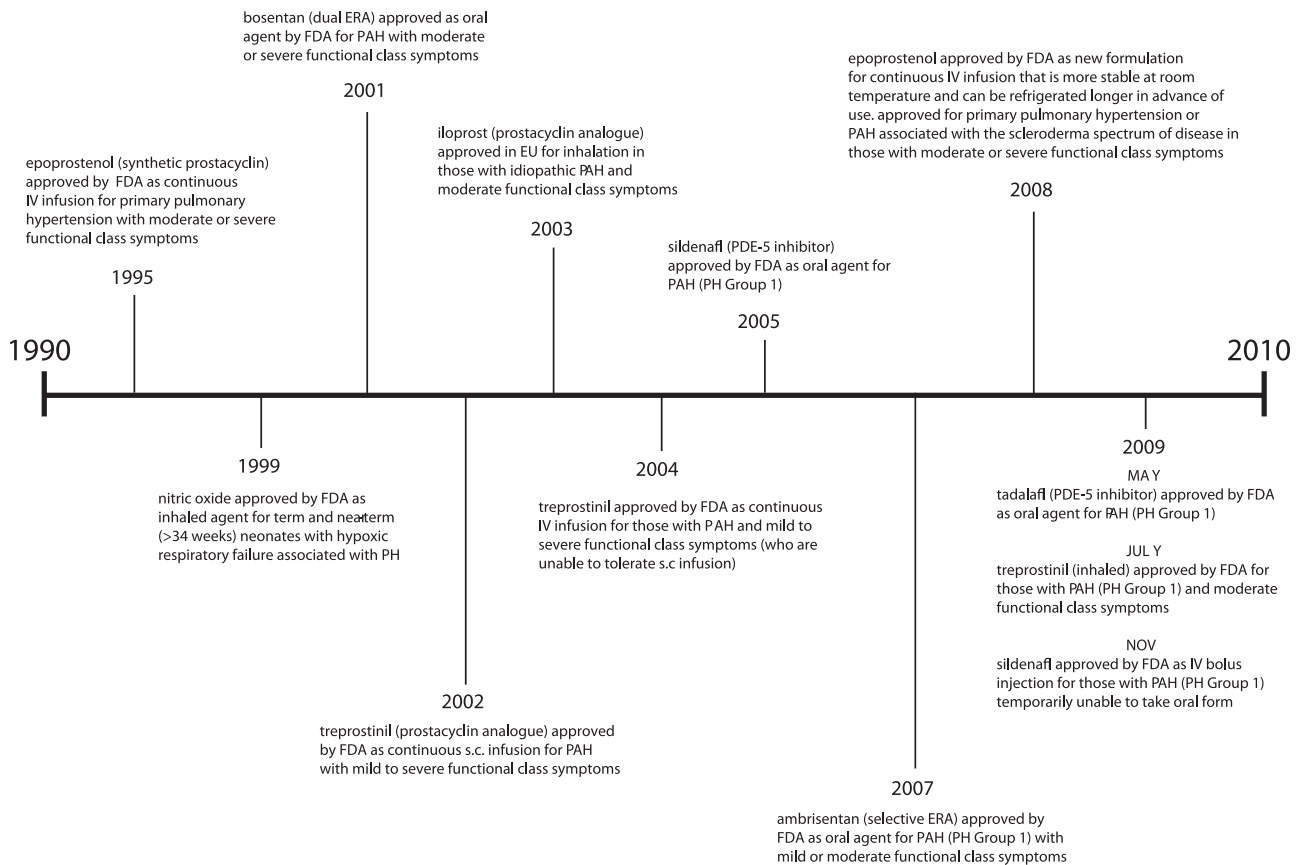


FIG. 3. Timeline of first approval of drugs (and their different formulations) currently used for PAH in North America or the EU.

rate of clinical worsening in patients with PAH in WHO functional classes III and IV. Because of risk of toxicity, bosentan is available in the United States only through a restricted distribution program that monitors liver function enzyme values and pregnancy status on a monthly basis. Subsequent approvals have occurred in more than 50 regions. In Canada and the EU, the initial indication was more restrictive than in the United States, reflecting the predominant study population enrolled in the pivotal bosentan trial: PAH that is idiopathic or associated with scleroderma and WHO functional class III symptoms. In 2006, the label was extended in Canada to include patients with either PAH related to HIV infection or congenital heart disease (functional class III or IV status) and in the EU to include patients with PAH related to congenital systemic-to-pulmonary shunts or Eisenmenger syndrome (class III status). In the EU (in 2008) and the United States and Canada (in 2009), the label was further revised to include patients with mild (class II) symptoms. In 2009, the EU label was expanded to include a pediatric dispersible formulation.

5. Ambrisentan. Ambrisentan is an oral selective ET_A -receptor antagonist approved in the United States in 2007. The drug was indicated as a once-daily treatment for patients with PAH and WHO functional class II (mild) or III (moderate) symptoms to improve exercise

capacity and delay clinical worsening. Ambrisentan was later approved for use in Canada (in 2008), EU (2008), New Zealand (in 2009), Australia (in 2009), and Japan (in 2010). A subsequent U.S. label revision specified treatment of patients with PAH regardless of functional status. Ambrisentan was initially dispensed in the United States only to patients through a restricted distribution program that monitored liver function enzyme values and pregnancy status on a monthly basis (as is the case with bosentan). In 2011, the FDA removed the requirement for monthly monitoring of liver function values with ambrisentan as a result of additional data reporting no significant increase in hepatic toxicity compared with patients with PAH not receiving an ERA. As a result, ambrisentan requires restricted distribution solely for pregnancy monitoring in women of childbearing potential because of risk of drug-related teratogenicity.

6. Nitric Oxide. NO is a potent pulmonary vasodilator that can be rapidly delivered to the lung by inhalation. Nitric oxide (INO_{max}) for inhalation was approved by the FDA in 1999 for term and near-term (older than 34 weeks' gestation) neonates with hypoxic respiratory failure and PPHN. In 2001, approval in the EU was obtained and subsequently expanded to include patients with peri- and postoperative PH in conjunction to cardiac surgery.

7. *Sildenafil*. Sildenafil is an oral PDE-5 inhibitor initially developed and marketed for erectile dysfunction (trade name Viagra). Sildenafil (trade name Revatio) was approved in 2005 as a thrice-daily therapy for PAH by the FDA and European Medicines Agency (EMA). Subsequent approvals have occurred in over 50 countries. In the United States, sildenafil is indicated for patients with PAH regardless of functional class. In the EU, sildenafil use is restricted to the predominant population studied in the pivotal phase 3 trial: patients with PAH that is either idiopathic or associated with connective tissue disease in functional class II (mild) or III (moderate). Sildenafil is also approved as an intravenous injection for patients who are temporarily unable to take oral sildenafil and in the EU as an oral suspension for the treatment of patients with PAH aged 1 to 17 years.

8. *Tadalafil*. Tadalafil is also an oral PDE-5 inhibitor, approved in 2009 in the United States and EU (and in 2010 in Canada and Japan) as a once-daily therapy to improve exercise capacity in patients with PAH. The EU label specifies use in those with mild to moderate functional class, reflecting the predominant phase 3 pivotal study population.

B. Additional Therapies and Approaches

Conventional therapy for PAH has included oral anticoagulation, supplemental oxygen, diuretics, and digoxin, although their use has not been evaluated in randomized controlled clinical studies. Microscopic thrombi have been observed in postmortem lung tissue of patients with idiopathic PAH (Fuster et al., 1984), and idiopathic PAH has been associated with a hypercoagulable state (Tournier et al., 2010). Although benefits of anticoagulation use have been reported mainly in those with idiopathic PAH and PAH associated with anorexigen use, and observational studies have led to conflicting conclusions (Johnson et al., 2012), long-term anticoagulation is believed to improve survival (Frank et al., 1997; Johnson et al., 2006). Hypoxia is a potent vasoconstrictor of the pulmonary vasculature, and supplemental oxygen is recommended to maintain oxygen saturation greater than 92% during sleep; ambulatory oxygen may benefit those with correctable desaturation on exercise (Galié et al., 2009b).

Calcium-channel blockade is very effective in some patients with PAH who respond favorably with acute vasodilator testing using epoprostenol or inhaled NO [e.g., decrease in mean pulmonary artery pressure (mPAP) of at least 10 mm Hg to a nadir \leq 40 mm Hg with no clinically significant decrease in cardiac output] (Barst et al., 2009). Most acute responders have been observed among those with idiopathic or heritable PAH; overall, approximately 8% of adults with idiopathic or heritable PAH respond favorably to acute vasodilator testing. Recommended calcium channel blockers for PAH are limited to nifedipine, amlodipine, and dilti-

azem; verapamil is not used because of its potential for negative inotropy (Young et al., 1983; Packer et al., 1984). In the absence of acute vasodilator testing, calcium channel blockers should not be used empirically in patients with PAH (Barst et al., 2009).

Patients not responding to medical therapy may be candidates for atrial septostomy or transplantation (lung or heart-lung). Atrial septostomy has been used as a bridge to transplantation because of the high mortality rate of patients with PAH on the transplant waiting list (Kerstein et al., 1995; Chen et al., 2009). Indications for atrial septostomy have generally been recurrent syncope or near-syncope or clinically significant right ventricular failure despite maximum medical therapy as appropriate for a given patient. Atrial septostomy is used most often in countries in which PAH-specific therapies are limited or unavailable. When the procedure is performed in experienced centers and in appropriately selected patients, improved functional class and survival have been reported (Rothman et al., 1999; Sandoval et al., 2011). The 5-year survival rate after transplantation in adult patients with PAH has historically been estimated at between 50 and 60% (Christie et al., 2011; de Perrot et al., 2012), with similar estimates for children (Benden et al., 2011; Goldstein et al., 2011).

The REVEAL Registry (55 U.S. PH centers) showed that nearly half of patients with PAH were receiving more than one PAH-specific therapy (Badesch et al., 2010). There is strong rationale for add-on combination therapy in PAH (Simonneau et al., 2008; Galié et al., 2009b; Galié et al., 2009c), despite limited data and lack of knowledge regarding whether any observed incremental benefit would have occurred if one medication replaced the other rather than being added to the other (McLaughlin et al., 2011). Combination studies to date, although few in number, have generally shown additive or synergistic benefit when targeting multiple pathways (Barst et al., 2009; Galié et al., 2009b; McLaughlin et al., 2009). Consensus treatment guidelines recommend combination therapy for patients with PAH who fail to show adequate improvement or who deteriorate with monotherapy. These guidelines also suggest that first-line combination therapy rather than sequential combined therapy may be useful for selected patients presenting with advanced disease (Hoepfer et al., 2005; Galié et al., 2009b,c; Kemp et al., 2012).

Although the advent of earlier diagnosis and therapy has increased the survival of patients with PAH, the disease remains progressive, debilitating, and ultimately fatal (McLaughlin et al., 2009; Benza et al., 2010b).

C. Approved Drugs

1. Epoprostenol

a. *Mechanism of action*. Prostacyclin (prostaglandin I_2), an eicosanoid, is derived from arachidonic acid primarily in the vascular endothelium. Prostacyclin is a

potent vasodilator and inhibitor of platelet aggregation (Smyth et al., 2009). These biologic effects are mainly mediated through specific G-protein-coupled receptors that generate cAMP (Narumiya et al., 1999). Prostacyclin can also inhibit growth of smooth muscle and have anti-inflammatory effects (Jones et al., 1995; Schrör and Weber, 1997; Olschewski et al., 2004; Hassoun et al., 2009), additional features that should be advantageous for PAH. Prostacyclin synthase (the enzyme involved in prostanoid biosynthesis) is decreased in the small- and medium-sized pulmonary arteries of patients with PAH (Tuder et al., 1999). In addition, evaluation of urinary metabolites suggests that PAH is associated with a decrease in the release of prostacyclin (and an increase in the release of the arachidonic acid metabolite thromboxane A_2 , which promotes vasoconstriction and platelet activation) (Christman et al., 1992).

b. Clinical studies. The synthetic prostacyclin epoprostenol is rapidly hydrolyzed at physiological temperature and pH and subject to enzymatic degradation, with an in vivo half-life in human blood estimated to be approximately 3 to 6 min and necessitating continuous infusion. Epoprostenol is one of the most effective therapies for PAH but is limited as a result of adverse events that include risks of clinically significant central venous line infections (including bacteremia and sepsis) and thromboembolic events. As a result, epoprostenol is most often reserved for those with severe (class IV) functional status or who retain moderate (class III) functional status despite use of at least two PAH-specific oral or inhaled drugs.

Initial approval of epoprostenol by the FDA in 1995 for patients with primary pulmonary hypertension and moderate-to-severe functional status was based on submission by Burroughs-Wellcome (Research Triangle Park, NC) of nine clinical studies, two controlled and seven uncontrolled. The largest multicenter controlled trial evaluated 81 adults with primary pulmonary hypertension and functional class III or IV status, despite optimal medical therapy (Barst et al., 1996). Subjects were treated for 12 weeks with continuously infused epoprostenol plus conventional therapy or conventional therapy alone (calcium channel blockade or supplemental oxygen if clinically indicated, cardiac glycosides, diuretic agents, and anticoagulants).

The 6-min walk test (distance walked by a patient on a hard, flat surface in 6 min) has been used as the primary efficacy measure in pivotal trials of all approved PAH therapies to date, either singly or as part of a composite endpoint (Galié et al., 2009b; McLaughlin et al., 2009). The test is unencouraged and is technically simple, inexpensive, reproducible, and well standardized (Enright 2003; ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Distance walked in 6 min has predicted morbidity as well as survival in patients with idiopathic, heritable, and anorexigen-associated PAH (Miyamoto et al., 2000;

Paciocco et al., 2001; Hoeper et al., 2004; Thenappan et al., 2012).

Table 2 shows that epoprostenol plus conventional therapy for 12 weeks, compared with conventional therapy alone, significantly improved exercise capacity as measured by 6-min walk distance. Mean change from baseline for 6-min walk distance was an increase of 32 m for patients receiving epoprostenol and a decrease of 15 m in patients receiving conventional therapy alone (treatment effect, 47 m; $P < 0.003$). Median change from baseline for 6-min walk distance was an increase of 31 m for patients receiving epoprostenol and a decrease of 29 m in patients receiving conventional therapy alone ($P < 0.002$; data not shown). In addition, epoprostenol (compared with conventional therapy alone) significantly improved both quality of life and functional class status. Because of the invasive drug delivery system, central venous lines were not inserted in those receiving conventional therapy alone, and persons blinded to the treatment assignments and presence of these lines conducted the efficacy assessments.

Epoprostenol also improved key cardiopulmonary variables after 12 weeks of treatment. Statistically significant improvements in cardiac index, stroke volume, systemic arterial oxygen saturation, mPAP, and pulmonary vascular resistance (PVR) were reported in patients receiving epoprostenol compared with those who did not. Mean changes in mPAP were -8% for the epoprostenol group versus 3% for the control group ($P < 0.002$); mean changes in PVR were -21% for the epoprostenol group versus 9% for the control group ($P < 0.001$). Cardiopulmonary hemodynamic changes in patients with PAH have prognostic value (D'Alonzo et al., 1991), independently predict survival (Thenappan et al., 2010), and correlate with change in 6-min walk distance (United States Food and Drug Administration, 2010).

Epoprostenol use has been consistently associated with improved survival. At the end of the 12-week treatment period, 8 of the 40 patients (20%) receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died ($P = 0.003$). Although the trial was not placebo-controlled or fully blinded, it remains the only randomized, controlled trial to show a survival benefit in patients with PAH. Subsequently, a large volume of clinical experience and observational data further support a survival benefit with use of epoprostenol. An open-label observational study in

TABLE 2
Exercise capacity (6-min walk distance) during continuous administration of epoprostenol for 12 weeks to patients with PAH
Data are from Barst et al. (1996) and are presented as mean \pm S.D.

	Epoprostenol Therapy (n = 41)	Conventional Therapy (n = 40)	P
	<i>m</i>		
Baseline	316 \pm 18	272 \pm 23	
Week 12	348 \pm 17	257 \pm 24	
Mean change from baseline	32	-15	<0.003

162 patients with idiopathic PAH who were treated long-term and followed for a mean of 36 months (median, 31 months) showed that survival was 87.8, 76.3, and 62.8% at 1, 2, and 3 years, respectively (McLaughlin et al., 2002). This survival is significantly greater than that expected on the basis of historical survival data before the availability of PAH-specific drugs (D'Alonzo et al., 1991). Improved long-term survival with epoprostenol therapy, compared with historical control subjects, has also been reported for 178 patients with idiopathic PAH followed for a mean period of 26 ± 21 months (range, 0.5–98 months) (Sitbon et al., 2002) and in a smaller cohort of 69 patients (18 followed for greater than 330 days) with idiopathic PAH and moderate to severe symptoms (Shapiro et al., 1997).

Common side effects of epoprostenol therapy are jaw pain, headache, flushing, nausea, and diarrhea. Serious side effects include systemic hypotension, central venous line-related infections (including sepsis), and thromboembolic events, including pulmonary embolism and stroke. Abrupt discontinuation of epoprostenol can lead to rebound PAH, with clinical worsening or death.

After initial approval, the U.S. epoprostenol (Flolan) label was revised to include patients with PAH associated with scleroderma (and moderate to severe symptoms) on the basis of a subsequent randomized, controlled trial showing improved exercise capacity and cardiopulmonary hemodynamics. In an open-label study of 111 adults with PAH associated with the scleroderma spectrum of disease, epoprostenol plus conventional therapy for 12 weeks significantly improved 6-min walk distance (median between-group change at week 12, 108 m, $P < 0.001$) and cardiopulmonary hemodynamics compared with those receiving conventional therapy alone (Badesch et al., 2000). An open-label uncontrolled observational 3-year extension study that evaluated 102 of these patients (56 who received epoprostenol and 46 who were receiving conventional therapy alone in the 12-week study) reported that epoprostenol improved survival compared with natural history data (Badesch et al., 2009).

Recognizing that epoprostenol is probably effective for a variety of causes of PAH beyond those comprising the clinical studies supporting approval, the U.S. Flolan label was further revised in 2011 to include the treatment of all group 1 PAH subgroups. The label emphasizes, however, that studies establishing effectiveness included predominantly patients with NYHA functional class III or IV symptoms and causes of idiopathic or heritable PAH or PAH associated with the scleroderma spectrum of diseases.

Epoprostenol is not approved for use in children. However, similarities between adult and pediatric PAH and compelling observational data (Yung et al., 2004; Lammers et al., 2007) have led to a consensus that epoprostenol provides significant benefit in children with idiopathic PAH, heritable PAH, and PAH associated with

congenital heart disease (Barst et al., 2011a). As with adults, line dislodgement, local infection, and sepsis remain significant concerns (Doran et al., 2008; Ivy et al., 2009).

c. Special considerations. The optimal dose of epoprostenol varies but is usually between 25 and $40 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for adults (McLaughlin et al., 2011); higher doses of 60 to $140 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ seem to be needed for children (Barst et al., 1999). For both children and adults, the infusion is usually started at $2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and increased incrementally, titrating side effects against efficacy. The dose is most rapidly increased during the first several months, with continued dose increases over the first year more slowly. Further increases have rarely shown benefit in adults but increases past the first year have not infrequently resulted in further improvement in pediatric patients (Barst et al., 1999).

The drug is provided as a freeze-dried preparation that needs to be dissolved in alkaline buffer, and patients must constitute the drug in sterile conditions daily. Because of its limited stability (8 h at room temperature) and short half-life (3–6 min), epoprostenol must be maintained in a refrigerated state and must be given by continuous infusion through a central venous catheter via a portable pump. Epoprostenol was the first PAH-specific treatment and many still regard it as the most effective approved therapy; however, it is cumbersome, inconvenient to use, and has significant potential safety concerns. Nevertheless, virtually all patients with PAH treated with epoprostenol improve, although the range of benefit can be extremely variable. Epoprostenol is used to increase not only survival but also overall quality of life. Epoprostenol is currently usually reserved for patients with severely impaired functional status or rapidly progressive PAH as well as patients who remain in moderate functional class despite treatment with combination oral and inhaled drugs. Use of epoprostenol in pediatrics is often more aggressive on the basis of limited data suggesting that early aggressive treatment (started early in life when the lung can continue to grow and at least until age 6–8 years) can permit ultimate transition to oral or inhaled therapy alone in select children (Melnick et al., 2010).

d. Commercial considerations. The generic exclusivity period for Flolan expired in 2007 (GlaxoSmithKline, Brentford, UK). In 2008, the FDA approved the first generic version of epoprostenol (Teva Pharmaceuticals, Jerusalem, Israel). In 2008, the FDA also approved a new continuous intravenous formulation of epoprostenol that is stable at room temperature for up to 24 h after dilution and may be stored up to 5 days at refrigerator temperature before use (GeneraMedix Inc., Liberty Corner, New Jersey). This formulation is indicated for the treatment of PAH that is idiopathic or associated with the scleroderma spectrum of disease in NYHA class III and IV patients who do not respond adequately to con-

ventional therapy. In 2009, GeneraMedix Inc. sold this formulation to Actelion, which began to market the drug (under the brand name Veletri) in April 2010. In late 2010, the Veletri label was expanded to allow medication preparation up to 7 days at refrigerator temperature or up to 48 h at room temperature in advance of use. Veletri has stable efficacy compared with Flolan, and offers improved convenience (e.g., mixing once weekly, infusion at room temperature without need for ice packs) as a result of its thermostability.

The annual cost of continuous intravenous delivery of epoprostenol can exceed U.S. \$100,000, depending upon patient (weight-based) dosing. Data from the Massachusetts Executive Office of Health and Human Services (2011) showed that as of early 2011, the average cost per claim reflected annual expenses between U.S. \$32,726 and \$131,048 for Flolan, and approximately \$35,000 for Veletri. The average wholesale price (AWP) for Veletri is generally more expensive than Flolan, and generic epoprostenol is less expensive than Flolan.

2. Treprostinil

a. Mechanism of action. Treprostinil, a prostacyclin analog with a terminal elimination half-life of approximately 2 to 4 h and a distribution half-life of approximately 40 min, is marketed by United Therapeutics (Silver Spring, MD). Treprostinil is administered either by inhalation, by a microinfusion pump for continuous subcutaneous infusion, or by a pump for continuous intravenous infusion. The latter can be given through either a pump similar to that used for epoprostenol or a much smaller infusion pump using a very concentrated dilution.

Unlike epoprostenol, treprostinil is chemically stable at room temperature and neutral pH. Similar to prostacyclin, analogs are considered to be vasodilators, inhibitors of platelet aggregation, and have some antiproliferative and anti-inflammatory effects (McLaughlin et al., 2009; Yang et al., 2010). Treprostinil is mainly metabolized by the liver (CYP2C8) and does not inhibit or induce major cytochrome P450 (P450) enzymes.

b. Clinical studies (subcutaneous infusion). Treprostinil (Remodulin) was approved by the FDA in 2002 for continuous subcutaneous infusion on the basis of two 12-week randomized, double-blind, placebo-controlled trials that were identical in design and conducted simultaneously.

The two controlled studies evaluated a combined 470 adults with functional class II to class IV status and PAH that was idiopathic, related to connective tissue disease, or related to congenital systemic-to-pulmonary shunts (Simonneau et al., 2002). Subjects received either subcutaneous treprostinil ($n = 232$) or placebo ($n = 236$) infusion. Treprostinil was started at $1.25 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, with dose adjustments after week 1 balancing efficacy and side effects (the dose averaged $9.3 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at week 12).

Compared with placebo, treprostinil improved median 6-min walk distance from baseline to week 12, but the improvement was only modest and not significant when each trial was analyzed separately ($P = 0.0607$ and 0.055). When data from both studies were pooled, treprostinil significantly improved 6-min walk distance (10-m median change from baseline to week 12 with treprostinil and no change with placebo; 16-m median difference between groups at week 12) (United States Food and Drug Administration, 2001; Simonneau et al., 2002). When 6-min walk distance was analyzed by quartile of treprostinil dose achieved at week 12, a marked dose response occurred with mean change in baseline of 36.1 m for the highest quartile ($>13.8 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) (Fig. 4).

In each study (and with pooled data), treprostinil significantly improved dyspnea and a symptom assessment that combined walking distance with measures of dyspnea. Data pooled for the two studies also showed small but significant changes in several cardiopulmonary hemodynamic parameters, including mPAP, PVR, mean right atrial pressure, cardiac index, and mixed venous oxygen saturation (Simonneau et al., 2002). Mean (\pm S.E.) change from baseline in mPAP at study end was

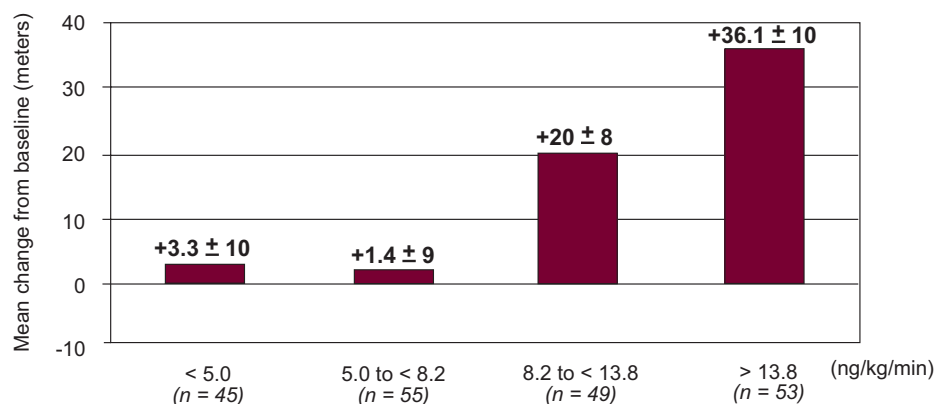


FIG. 4. Mean (\pm S.E.) change in the 6-min walk distance from baseline to week 12 versus week 12 treprostinil dose quartile. [Reprinted from Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, et al. (2002) Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 165:800–804. Copyright © 2002 American Thoracic Society. Used with permission.]

-2.3 ± 0.5 mm Hg (-3%) for treprostinil-treated patients and 0.7 ± 0.6 mm Hg (1%) for placebo-treated patients.

The most common adverse events noted in treprostinil-treated patients were infusion site pain (85% treprostinil versus 27% placebo), infusion site reaction (83 versus 23%), and headache (27 versus 23%). Eighteen patients (8%) discontinued treprostinil because of injection site pain (compared with one receiving placebo); local infusion site pain was considered dose-limiting and resulted in a low dose of treprostinil achieved by week 12 in most patients. Subsequent studies have shown that these local adverse events considered dose-limiting in this pivotal trial (of pooled data) can be transient and are not dose-related, suggesting that the trial resulted in less efficacy than would have been expected if higher doses were used (Mathier et al., 2010). Indeed, the protocols of the two pivotal studies did not allow dosing above $22.5 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over the 12-week period; compared with later trials that evaluated doses greater than $40 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Lang et al., 2006), patients in these trials were exposed to low doses of drug.

The relationship between increasing dose beyond that achieved in the pivotal treprostinil (subcutaneous) trials and resultant efficacy is best supported by data from a multicenter retrospective study of 99 patients with PAH and 23 patients with chronic thromboembolic pulmonary hypertension (CTEPH). At approximately 3 years, mean \pm S.E. change from baseline for 6-min walk distance was 65 ± 38 m in 49 patients who achieved a mean treprostinil dose of around $40 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Lang et al., 2006). In this long-term observational study, infusion site pain—reported by most patients—did not seem to be dose-related and caused discontinuation of treatment in only six patients (4.9%).

Long-term treatment with treprostinil given subcutaneously seems to improve survival. Barst et al. (2006a) reported results from an open-label study evaluating 860 adults with idiopathic (48%) and associated PAH (52%): 423 patients who received treprostinil monotherapy in both the aforementioned pivotal trials (Simonneau et al., 2002) and another placebo-controlled study (McLaughlin et al., 2003) and an additional 437 de novo patients. Continuous subcutaneous infusion of treprostinil was administered to 538 (63%) patients for 1 year, 312 (36%) patients for 2 years, 135 (17%) patients for 3 years, and 13 (2%) patients for 4 years. Of the initial 860 patients, 199 (23%) discontinued because of adverse events, 136 (16%) died, 117 (14%) discontinued because of clinical worsening, 29 (3%) withdrew consent, and 11 (1%) underwent transplantation. A total of 97 patients (11%) switched from subcutaneously administered treprostinil to an alternative prostacyclin analog; bosentan was added in 105 patients (12%) and sildenafil in 25 (3%). Survival was 87 to 68% over 1 to 4 years for all 860 patients and 88 to 70% over 1 to 4 years for those receiving only treprostinil monotherapy. For the sub-

group of patients with idiopathic PAH and baseline hemodynamics ($n = 332$), survival was 91 to 72% over 1 to 4 years. In contrast, predicted survival, on the basis of the early U.S. National Institutes of Health Registry that enrolled untreated patients with idiopathic PAH, was 69 to 38% over 1 to 4 years (D'Alonzo et al., 1991). Therefore, use of (subcutaneous infusion) treprostinil is—similar to epoprostenol—also associated with improved survival and in observational cohorts that are considerably larger in patient number than with epoprostenol.

The initial approval of treprostinil in the United States as a continuous subcutaneous infusion was for the treatment of PAH (regardless of cause) in patients with mild to severe (class II–IV) symptoms. Treprostinil was subsequently approved (and launched) in more than 35 regions, including most EU member countries.

In early 2006, the FDA expanded the (subcutaneous) treprostinil label to include patients transitioning from epoprostenol. This label change was based on an 8-week randomized, double-blind, placebo-controlled study of patients with PAH who were randomly transitioned from stable doses of intravenous epoprostenol to either subcutaneous treprostinil ($n = 14$) or subcutaneously administered placebo ($n = 8$) (Rubenfire et al., 2007). The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in epoprostenol dose during the transition period, hospitalization as a result of PAH, or death. Treprostinil significantly prevented clinical deterioration in patients transitioning from epoprostenol therapy compared with placebo. Seven of 8 patients (88%) withdrawn to placebo had clinical deterioration, whereas only 1 of 14 patients (7%) withdrawn to treprostinil had clinical deterioration ($P = 0.00023$ on the basis of treatment comparison of time to deterioration). In 2011, the treprostinil label was further revised by the FDA to include all subgroups of patients with PAH (PH group 1), regardless of functional class. In contrast, treprostinil given as a subcutaneous infusion is approved in most of Europe for the treatment of idiopathic or heritable PAH in those with functional class III symptoms.

Treprostinil is not approved for use in children, and data from this population are limited. Small uncontrolled studies suggest that children with PAH may benefit when treprostinil given subcutaneously is either added to background therapy (Levy et al., 2011) or when patients can be safely transitioned from intravenous epoprostenol to intravenous treprostinil (Ivy et al., 2007).

c. Clinical studies (intravenous infusion). In 2004, the FDA and Health Canada approved a formulation of treprostinil (Remodulin) for continuous intravenous infusion in patients with PAH and functional class II to class IV (mild to severe) disease who cannot tolerate the subcutaneous form (or in whom the risks of the delivery system is warranted). Subsequent approval has oc-

curred in most of the EU. In contrast to 8 or 12 h for epoprostenol, the intravenous infusion reservoir system can be changed every 48 h with treprostinil.

Approval was based on bioequivalence between the two formulations at steady state (Laliberte et al., 2004) and a 12-week prospective open-label study of 31 adults with PAH who were switched from intravenous epoprostenol to intravenous treprostinil over 24 to 48 h (Gomberg-Maitland et al., 2005). The transition seemed safe and had efficacy similar to that of intravenous epoprostenol. Subsequent open-label (Tapson et al., 2006) and placebo-controlled (Hiremath et al., 2010) trials have shown that 12 weeks of treatment with intravenous treprostinil resulted in significant and clinically meaningful improvement in exercise capacity and cardiopulmonary hemodynamics.

As a result of reports of Gram-negative bloodstream infection occurring among outpatients who received intravenous treprostinil, and at a rate that exceeded that of intravenous epoprostenol (Kallen et al., 2008), the U.S. label was revised in 2008 to emphasize that continuous intravenous infusion can include serious bloodstream infection because of the risks associated with chronic indwelling central venous catheters. This increased risk of Gram-negative infection may be due in part to mixture of intravenous treprostinil in a pH-neutral saline diluent; this risk seems to be minimized by using the alkaline epoprostenol diluent for intravenous treprostinil rather than the saline diluent initially recommended (Rich et al., 2012).

d. Clinical studies (inhalation). In 2009, United Therapeutics received FDA approval for inhaled treprostinil (Tyvaso) in patients with PH group 1 (PAH) and functional class III (moderate) symptoms on the basis of the data from the single pivotal trial TRIUMPH-1 (McLaughlin et al., 2010). TRIUMPH-1 randomized 235 adults with PAH and functional class III (98%) or IV symptoms to receive 4 daily inhalations of treprostinil or placebo added to background bosentan (ERA) (67%) or sildenafil (PDE-5 inhibitor) (33%) therapy for 12 weeks. Treprostinil improved the placebo-corrected median change from baseline in peak 6-min walk distance by 20 m at week 12 ($P = 0.0004$). Subgroup analyses showed a more pronounced treatment effect for patients receiving background bosentan therapy compared with sildenafil therapy (although there were fewer patients receiving background sildenafil than background bosentan, and the study was not powered for subgroup analyses). Quality of life significantly improved on two subscales, but there were no improvements in time to clinical worsening, Borg dyspnea score, functional class, and PAH signs and symptoms. The most common adverse events, occurring in $\geq 10\%$ of treprostinil-treated patients, were cough (54% treprostinil versus 29% placebo), headache (41 versus 23%), throat irritation or pharyngolaryngeal pain (25 versus 14%), nausea (19 versus 11%), dizziness (17 versus 15%), and flushing (15

versus $<1\%$). Twenty-three patients prematurely discontinued the study (10, placebo; 13, treprostinil); the most common reasons for discontinuation were withdrawal of consent among patients receiving placebo and adverse events among patients receiving treprostinil.

An open-label extension trial that enrolled 206 patients (88%) who participated in the controlled trial (TRIUMPH-1) reported continued benefit from treprostinil, including significant improvement in median 6-min walk distance (18 m) for the 118 patients who continued to receive treprostinil for 24 months (Benza et al., 2011).

A condition of FDA approval of inhaled treprostinil was for United Therapeutics to conduct a postmarketing study confirming efficacy and a long-term observational study evaluating the risk of oropharyngeal (mainly pharyngolaryngeal pain) and pulmonary toxicities (United Therapeutics, 2009). Both studies are ongoing. In 2009, the marketing application for inhaled treprostinil was withdrawn in Europe after the EMA noted that operational issues at two investigative sites would preclude approval (United Therapeutics, 2009).

Inhaled treprostinil has had limited use in pediatrics; however, it seems to be easier to administer than inhaled iloprost, even in children as young as 3 to 4 years, because of its simpler delivery system. The four-times-daily dosing with inhaled treprostinil (versus 6–9 times daily with iloprost) is another advantage in school-age children.

e. Oral treprostinil. United Therapeutics has completed a series of studies evaluating an oral formulation of treprostinil; to date, benefit has been shown in treatment-naïve patients (but not as an add-on to PAH-specific background therapy).

In 2008, a 16-week placebo-controlled trial (FREEDOM-C) of sustained release oral treprostinil in 350 adults receiving approved background therapy (ERA, PDE-5 inhibitor, or both) failed to achieve its primary endpoint of change in 6-min walk distance but experienced challenges with escalation of dosing above 1 mg twice daily (United Therapeutics, 2008; Tapson et al., 2009). Exploratory post hoc analyses of 6-min walk distance showed that patients who were able to achieve a dose of between 1.25 and 3.25 mg twice daily had a median improvement of 18 m, and patients achieving a dose of 3.25 to 16 mg twice daily had a median improvement of 34 m.

As a result, a second study (FREEDOM-C-2) of 310 patients was initiated in 2009 with a design similar to that of FREEDOM-C but involving a lower starting dose (0.25 mg twice daily) and use of concomitant ERA or PDE-5 inhibitor therapy (or both). In 2011, negative results were reported; treprostinil failed to significantly improve the primary endpoint of 6-min walk distance at week 16 (United Therapeutics, 2011a).

In 2011, results from a third trial (FREEDOM-M) were reported. This trial evaluated a low starting dose of

the oral formulation (0.25 mg twice daily) in an attempt to improve the tolerability over 12 weeks of treatment in 349 patients with PAH who were not receiving background therapy (Rubin et al., 2011; United Therapeutics, 2011b). Treprostinil significantly increased the median 6-min walk distance by 23 m in the 228 patients receiving treprostinil ($P = 0.0125$). Secondary efficacy endpoints (WHO functional class change, dyspnea index score, and time to clinical worsening) were not met. On the basis of the results of FREEDOM-M, a new drug application is under review by the FDA for the use of sustained release tablets of treprostinil for PAH (United Therapeutics, 2012).

The results of the FREEDOM studies illustrate the challenges of showing efficacy in trials of combination therapy. Chakinala (2009) has noted that smaller improvements in clinical trials of PAH therapies are to be expected because study populations have changed from treatment-naïve patients with advanced symptoms to less ill patients receiving combination therapy. The latter group is regarded as having attenuated treatment effects in clinical trials, even when baseline factors that predict efficacy are balanced in the same trial for those who are receiving background therapy and those who are not (Galié et al., 2009a). Trials of longer duration and use of open-ended event-driven or composite endpoints may be several options that could allow better detection of true treatment effects in clinical trials of patients receiving PAH-specific background therapy (Chakinala 2009). As with the initial pivotal (subcutaneous) treprostinil trials, the FREEDOM trials have also been limited by an inability to determine a priori which patients are able to tolerate higher doses and consequently achieve greater clinical benefit.

f. Commercial considerations. Treprostinil as a continuous subcutaneous infusion was initially approved for patients with PAH and mild to moderate functional class symptoms but is typically initiated in those with either moderate symptoms or those who have suboptimal response while receiving oral therapy (Mathier et al., 2010). The initial pivotal studies of subcutaneously administered treprostinil failed to achieve optimal dosing in most of the patients (Simonneau et al., 2002). Subsequent studies have shown that more rapid dose escalation does not increase infusion site pain, thereby allowing increased dosing and better efficacy (Skoro-Sajer et al., 2008; Mathier et al., 2010). The optimal dose varies between patients and has been reported to be between 20 and 80 ng · kg⁻¹ · min⁻¹ (Galié et al., 2009b). Treprostinil by subcutaneous infusion is expensive and is also dependent upon weight-based dosing. Data from the Massachusetts Executive Office of Health and Human Services (2011) showed that the average cost per claim for treprostinil injection in early 2011 represented annual expenses between U.S. \$59,396 and \$148,543.

In contrast to subcutaneously administered treprostinil, continuous intravenous treprostinil has not

gained as wide adoption, probably because of the subsequent approval of several oral therapies, expense, and limited patient population (primarily those unable to tolerate the subcutaneous form or who are being transitioned from intravenous epoprostenol). Continuously infused intravenous treprostinil also has an increased risk of infections (compared with epoprostenol), although this risk seems to be reduced by use of an alkaline diluent (Rich et al., 2012). The same treprostinil vials are used for subcutaneous and intravenous administration; differences in costs between patients with the two formulations do not reflect cost of the drug per se but are generally due to variances in dosing related to tolerability and increased expense associated with intravenous catheter maintenance. Although nearly all patients transitioned from intravenous epoprostenol to intravenous treprostinil remain stable, there are rare patients who deteriorate after transition (observational cases); furthermore, there are rare patients who are receiving intravenous treprostinil without prior intravenous epoprostenol who do not adequately improve when receiving intravenous treprostinil but do improve with transition from the intravenous treprostinil to intravenous epoprostenol (Walkey et al., 2011).

Treprostinil administered by inhalation is estimated to cost up to U.S. \$150,000 annually (Red Book, 2010); data from the Massachusetts Executive Office of Health and Human Services (2011) showed that the average cost per claim for inhaled treprostinil in early 2011 represented an annual expense of approximately \$142,000. Inhaled treprostinil has some practical advantages compared with the other approved inhaled prostacyclin analog, iloprost (Ferrantino and White, 2011). Treprostinil is initially administered four times a day by inhaling up to nine breaths during each 2- to 3-min treatment session; this frequency of administration is considerably less than that of iloprost (six to nine times daily). In addition, a day's supply of inhaled treprostinil is packaged in a single ampoule emptied into the nebulizer once a day, which requires cleaning only once a day (in contrast to iloprost). Preliminary data from an interim analysis of 55 patients showed that rapid transition from inhaled iloprost to inhaled treprostinil was safe and seemed to result in further improvements in exercise capacity and quality of life after 12 weeks (Bourge et al., 2010).

The U.S. patent for the method of treating PAH with treprostinil infusion will expire in October 2014. The U.S. patents covering methods of synthesizing and producing treprostinil will expire in October 2017. United Therapeutics has been granted one patent in the EU and one patent in Japan, each of which covers the treprostinil synthesis and production methods and will expire in October 2018. The patent for inhaled treprostinil for the treatment of PAH will expire in the United States in 2018 and in various countries throughout the EU in 2020.

3. Iloprost

a. Mechanism of action. Iloprost, a synthetic analog of prostacyclin with a serum half-life of 20 to 25 min, can be delivered by inhalation and dilates the systemic and pulmonary arterial vascular beds. Iloprost can also be delivered via oral preparation and continuous intravenous infusion. As with other prostacyclin analogs, iloprost is believed to affect platelet aggregation and cell proliferation (Beghetti et al., 2002; Clapp et al., 2002). In vitro studies suggest that no clinically relevant inhibition of P450 metabolism by iloprost should be expected (Ventavis package insert, 2011).

b. Clinical studies. Initially developed by Schering AG (Berlin, Germany), iloprost as an inhalation (Ventavis) is approved in the EU and Australia for patients with idiopathic PAH and functional class III (moderate) symptoms, and in the United States for patients with PH group 1 PAH.

After EU approval in 2003, Schering sold its iloprost rights in the United States to CoTherix (South San Francisco, CA). Subsequent FDA approval occurred in 2004. In 2006, CoTherix was acquired by Actelion (Allschwil, Switzerland). In 2007, Bayer AG (Berlin) acquired Schering AG. Iloprost is currently marketed by Actelion in the United States and by Bayer Schering Pharma AG (Berlin) outside the United States.

Regulatory approvals of iloprost were based on one pivotal multicenter trial that was conducted in Europe and enrolled 203 adult patients with moderate or severe inoperable CTEPH or PAH that was idiopathic or associated with scleroderma or appetite-suppressant drugs (Olschewski et al., 2002). Patients received repeated iloprost inhalations of 2.5 or 5.0 μg (median inhaled dose, 30 μg per day) or placebo between six and nine times daily for 12 weeks. The primary endpoint was a combined measure of improvement of at least one functional class and at least 10% improvement in 6-min walk distance from baseline to week 12. The combined clinical endpoint was met by 17% of subjects receiving iloprost and 5% of subjects receiving placebo ($P < 0.05$). Figure 5 shows that iloprost significantly increased mean 6-min walk distance compared with placebo (36 m, $P = 0.004$).

Further effects of iloprost treatment included a significant improvement in cardiopulmonary hemodynamics, functional class, dyspnea, and quality of life (EuroQol scale). Iloprost was generally well tolerated; cough, headache, vasodilation (flushing), flu syndrome, and nausea were the most common adverse events.

In several European countries, iloprost (under trade name Ilomedine or Ilomedin) is also approved as a short-term intravenous infusion that can be repeated at periodic intervals in patients with conditions related to critical limb ischemia. Iloprost given as an intravenous infusion has not been approved for PAH outside of New Zealand but has had variable off-label use in Europe on the basis of observations of benefit in a small number of patients with PAH (Higenbottam et al., 1998). Random-

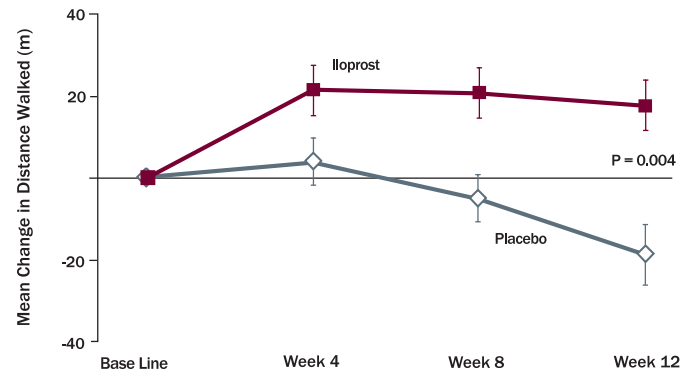


FIG. 5. Effect of inhaled iloprost and placebo on the mean (\pm S.E.) change from baseline in the 6-min walk distance. [Reprinted from Olschewski H, Simonneau G, Galié N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, et al. (2002) Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 347:322–329. Copyright © 2002 Massachusetts Medical Society. Used with permission.]

ized controlled trials evaluating use of intravenous iloprost for PAH have not been conducted (Provencher and Sitbon, 2009). An oral iloprost preparation has been used in investigational studies of Raynaud's phenomenon secondary to systemic sclerosis (Black et al., 1998); its value in PAH is not known.

Similar to other prostanoids, iloprost is not approved for use in children, and data on its use in the pediatric PAH population is limited. Ivy et al. (2008) evaluated use of inhaled iloprost in 22 children with a median age of 11.5 years (range, 4.5–17) and PAH that was idiopathic or related to congenital heart disease (19 receiving background PAH-specific therapy). After 6 months of treatment, WHO functional class improved in 35%, decreased in 15%, and remained unchanged in 50% of the children. In addition, therapy was limited in some children by drug-induced bronchoconstriction (not previously noted with adults) and poor compliance with multiple daily inhalations. A review of 28 studies (most case series) comprising 195 children suggests that inhaled iloprost has acute effects similar to those of inhaled NO and might have a role in the short-term treatment of pediatric PH, including neonates, especially in countries where inhaled NO is not available (Mulligan and Beghetti, 2011). However, failure to report dosing, wide differences in doses between studies, and use of several types of administration devices complicate determination of the best dosage of iloprost in these settings (Mulligan and Beghetti, 2011).

c. Commercial considerations. The label for inhaled iloprost in the EU (and Australia) is restricted to patients reflecting most of the pivotal study population: those with idiopathic PAH and functional class III (moderate) symptoms. In contrast, the current label in the United States and other regions is broader and includes those with PH group 1 PAH. The pivotal trial of iloprost showed significant improvement in the combined endpoint of functional class change and 6-min walk distance. However, the required six-to-nine-times-a-day ad-

ministration raises concerns about end-of-dose wearing off and the competitive market. Attempts to reduce the frequency of inhaled administration and development of an effective oral formulation have not been successful. The patent for iloprost expired in the United States in 2011; the patent in the EU is expected to expire in 2014.

To evaluate use of 16 weeks of inhaled iloprost with background sildenafil, a phase 3 trial of inhaled iloprost combined with oral sildenafil for the treatment of PAH was initiated. The trial, called VISION (Ventavis Inhalation with Sildenafil to Improve and Optimize Pulmonary Arterial Hypertension), was a double-blind, placebo-controlled trial of 180 patients with PAH receiving a stable dose of sildenafil. Patients were to be randomized to one of three groups (four daily doses of iloprost, six daily doses of iloprost, or placebo) for 16 weeks (<http://clinicaltrials.gov> identifier NCT00302211). The study was terminated in 2008 because of slow enrollment and underscores the challenges of both use of iloprost as a first-line (or even second-line) therapy and conducting randomized placebo-controlled trials with approved drugs. In 2009, Actelion announced a new formulation (20 μ g/ml) that allows the same inhaled dose (5 μ g) in half the inhaled volume. This change was to reduce inhalation time and increase patient compliance.

The estimated yearly U.S. cost of iloprost for inhalation is usually in excess of \$100,000 and varies on the basis of number of doses per day (AWP; Red Book, 2010); data from the Massachusetts Executive Office of Health and Human Services (2011) showed that the average cost per claim as of early 2011 for iloprost represented annual expenses between \$118,686 and \$134,955.

4. Bosentan

a. Mechanism of action. ET-1 is a potent endogenous vasoconstrictor that also stimulates pulmonary artery smooth muscle cell proliferation (Levin, 1995; Davie et al., 2002). The actions of ET-1 are mediated by two receptors, ET_A and ET_B. ET_A and ET_B receptors mediate vasoconstriction and vascular smooth muscle cell proliferation (Kedzierski and Yanagisawa, 2001). ET_B receptors, also present on endothelial cells, can potentially offset the action of ET_A receptors by increasing release of the vasodilator and antiproliferative modulators prostacyclin and NO and reducing clearance of ET-1 from the lung (Fukuroda et al., 1994; Kedzierski and Yanagisawa, 2001). The increased expression of ET-1 in patients with PAH is supported by numerous observations, including elevated plasma levels that correlated with the severity of disease in 16 patients with idiopathic PAH (Rubens et al., 2001). PAH has also been associated with increased levels of ET-1 mRNA and ET-1 peptide in the endothelial cells of pulmonary arteries (Giavid et al., 1993) and a reduced clearance of ET-1 in the pulmonary vasculature (Stewart et al., 1991). Use of ERAs for PAH may also result in greater benefit in women than men, and in whites compared with blacks (Gabler et al., 2012).

The pathophysiologic basis for these treatment-response differences is not known.

b. Clinical studies. Actelion (Allschwil, Switzerland) developed and markets bosentan (Tracleer), which is a specific and competitive antagonist of both ET_A and ET_B receptors and is the only approved orally active dual ERA. Bosentan has a terminal elimination half-life of approximately 5 h in healthy adults and is metabolized to active metabolites by an inducer of CYP2C and CYP3A (Tracleer package insert, 2011).

Approval of bosentan was based on two randomized, double-blind, placebo-controlled trials (Channick et al., 2001; Rubin et al., 2002). The initial pivotal trial (study 351) evaluated 32 patients with PAH that was idiopathic or associated with scleroderma and WHO functional class III (moderate) or IV (severe) symptoms (Channick et al., 2001). Patients were randomized to receive either bosentan (62.5 mg taken twice daily for 4 weeks then 125 mg twice daily, $n = 21$) or placebo ($n = 11$) for a minimum of 12 weeks. Figure 6 shows that bosentan significantly improved 6-min walk distance change from baseline to week 12 (mean placebo-adjusted change, 76 m; $P = 0.021$); this improvement was maintained through week 20. Bosentan resulted in a modest but statistically significant improvement in mPAP, cardiac index, and PVR (mPAP; mean change from baseline for bosentan, -1.6 mm Hg; placebo, 5.1 mm Hg; $P = 0.013$). Bosentan also significantly improved functional class status and time to clinical worsening compared with placebo. Increased liver enzyme values (undefined) were noted in two patients and returned to normal without discontinuation or dose change.

A second randomized, placebo-controlled trial (BREATHE-1) evaluated 213 patients with PAH (idiopathic or associated with connective tissue disease) and WHO functional class III or IV status at 27 centers in Europe, North America, Israel, and Australia (Rubin et al., 2002). Subjects were randomized to receive 1) bosentan 62.5 mg twice daily for 4 weeks followed by either 125 mg ($n = 74$) or 250 mg ($n = 71$) twice daily for 12 weeks or 2) placebo for 16 weeks ($n = 69$).

Pooled bosentan data for both doses (125 and 250 mg) showed a 44-m treatment effect for the primary efficacy endpoint of change in mean 6-min walk distance from baseline to week 16. Figure 7 shows that when data were evaluated by each dose group, the (placebo-adjusted) change in 6-min walk distance showed a difference between doses: 35 m with 125 mg twice daily and 54 m with 250 mg twice daily.

Bosentan (pooled data from both doses) also significantly improved functional class and reduced the time to clinical worsening at week 16 (clinical worsening was defined as death, lung transplantation, hospitalization for PAH, no improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy). Although the difference between each bosentan group and placebo for time to clinical worsen-

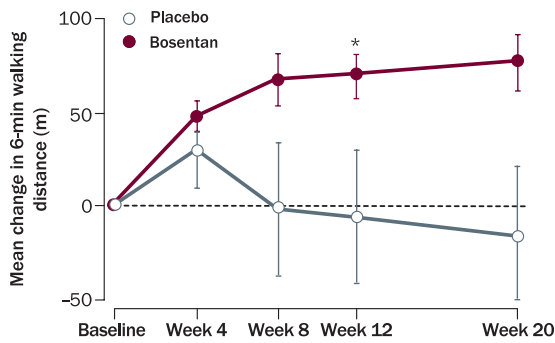


FIG. 6. Mean (\pm S.E.) change from baseline in the 6-min walk distance for bosentan ($n = 21$) and placebo ($n = 11$) groups. Patients who did not complete week 20 assessments (bosentan, $n = 1$; placebo, $n = 4$) had their last observed values carried forward. *, $P < 0.05$ versus baseline, $P = 0.021$ versus placebo at week 12. [Reprinted from Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, et al. (2001) Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 358:1119–1123. Copyright © 2001 Elsevier, Inc. Used with permission.]

ing was significant at weeks 16 and 28, the differences were greatest for the subset of subjects followed through week 28.

Elevated liver aminotransferase values greater than three times normal occurred in 21 of 165 subjects (12.7%) receiving bosentan, with a higher incidence in the group receiving 250 mg twice daily. Furthermore, elevated aminotransferase levels greater than eight times normal occurred in 7 of 165 subjects (4.2%) receiving bosentan, with two cases (2.1%) in the group receiving 125 mg twice daily and five cases (7.1%) in the group receiving 250 mg twice daily. There were no reports of clinical sequelae, including jaundice or liver failure. Despite a question of greater efficacy with 250 mg twice daily, the increased risk of hepatotoxicity resulted in approval of the lower dose of 125 mg twice daily.

The most common adverse events observed with bosentan treatment, and with greater frequency than placebo, were headache (21% pooled bosentan versus 19% placebo), flushing (9 versus 4%), syncope (9 versus 6%), and abnormal liver enzymes (9 versus 3%). Because of the risk of hepatotoxicity, FDA approval required patients to obtain liver function tests at least monthly through a restricted drug distribution program with either dose reduction, interruption of treatment, or permanent discontinuation depending upon aminotransferase values. Testing for pregnancy is also required monthly in women of childbearing potential.

c. Expansion of product label.

i. *Mild disease.* Bosentan was initially approved in the U.S. in 2001 for patients with functional class III and IV (moderate and severe) disease and in Canada and the EU for those with class III disease only. In 2008 (EU) and 2009 (Canada, United States), the label was expanded for patients with functional II (mild) symptoms on the basis of a randomized, placebo-controlled trial (EARLY). This trial evaluated exercise capacity and hemodynamics in 185 patients (16% receiving stable

doses of sildenafil) aged 12 or older with mild PAH who were treated for 6 months (Galie et al., 2008b). Bosentan resulted in significant improvement in PVR (-22.6% placebo-adjusted change from baseline, $P < 0.0001$) and a trend toward improvement in 6-min walk distance (placebo-adjusted increase of 19 m, $P = 0.07$).

ii. *Pulmonary arterial hypertension related to HIV infection.* In Canada, the initial bosentan label was restricted to the predominant study population in the pivotal trial (idiopathic or related to scleroderma; moderate symptoms) but later revised in 2006 to include those with PAH related to HIV infection. This revision was based on an open-label trial that evaluated the safety and efficacy of bosentan in 16 adults with PAH related to stable HIV infection, BREATHE-4 (Sitbon et al., 2004). All patients except one were receiving highly active antiretroviral therapy at baseline, consisting of a combination of at least three antiretroviral medications. Subjects received bosentan for 16 weeks (62.5 mg twice daily for 4 weeks, then 125 mg twice daily for 12 weeks). Down-titration was allowed for safety and tolerability, and all subjects except one received the maximum dose of bosentan (125 mg twice daily). Significant improvement was observed from baseline to week 16 for all efficacy parameters: 6-min walk distance (91-m improvement, $P < 0.001$), functional class (14 patients improved), hemodynamics (cardiac index increased by 39% and mPAP decreased by -21% , $P < 0.001$), echocardiograph indices, and quality of life. During the study, no patient died and none required epoprostenol (rescue) treatment. The most frequent adverse events were peripheral edema, headache, and abnormal liver function. Hepatic tolerability was similar to that reported for patients with other forms of PAH receiving bosentan. Bosentan had no apparent negative impact on control of HIV infection (CD4 count and plasma viremia). However, coadministration of the antiretroviral agents lopinavir/ritonavir with bosentan dramati-

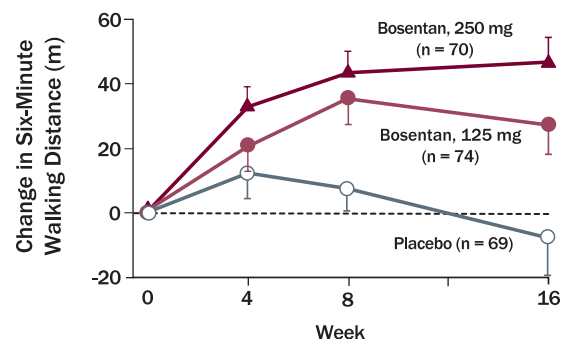


FIG. 7. Mean (\pm S.E.) change from baseline to week 16 in the 6-min walk distance for bosentan and placebo groups. $P < 0.01$ for the comparison between the 125-mg dose of bosentan and placebo, and $P < 0.001$ for the comparison between the 250-mg dose of bosentan and placebo. [Reprinted from Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, and Simonneau G (2002) Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 346:896–903. Copyright © 2002 Massachusetts Medical Society. Used with permission.]

cally increases bosentan levels (Dingemanse et al., 2010). Detailed adjustment of bosentan dosing must occur when any ritonavir-containing compound is concomitantly used (Tracleer package insert, 2011).

iii. Pulmonary arterial hypertension related to congenital heart disease. In 2006, the Canadian label was also expanded to include those with congenital heart disease (functional class III or IV status) and in the EU to include patients with PAH related to congenital systemic-to-pulmonary shunts or Eisenmenger syndrome (class III status). This revision was based on a multicenter, randomized, double-blind, placebo-controlled study conducted in 54 patients (12 years of age and older) with PAH related to Eisenmenger syndrome and WHO functional class III status, BREATHE-5 (Galié et al., 2006). Subjects were randomized two to one to bosentan ($n = 37$) or placebo ($n = 17$) for 16 weeks. Systemic pulse oximetry (primary safety endpoint) and PVR index (primary efficacy endpoint) were assessed by right- and left-heart catheterization. Secondary endpoints included exercise capacity assessed by 6-min walk distance and additional hemodynamic parameters. Bosentan treatment did not worsen oxygen saturation; the placebo-corrected effect of bosentan on systemic pulse oximetry was 1.0%. Bosentan resulted in significant and clinically meaningful (placebo-adjusted) improvement in PVR index ($-472.0 \text{ dyne} \cdot \text{s/cm}^5$, $P = 0.0383$), mPAP (-5.5 mm Hg , $P = 0.0363$), and exercise capacity (53.1 m ; $P = 0.0079$). Four patients discontinued because of adverse events: two (5%) in the bosentan group and two (12%) in the placebo group.

iv. Pediatric formulation. In 2009, the EMA approved a dispersible (disintegrates in water) formulation of bosentan (quadrisection 32-mg tablet) to be used for children above the age of 2 years. This revision was based on results from two open-label trials, BREATHE-3 and FUTURE-1. BREATHE-3 evaluated the tolerability and safety of 12 weeks of bosentan in children (<15 years of age) with PAH, some with concomitant epoprostenol use (Barst et al., 2003a). FUTURE-1 evaluated the safety and pharmacokinetics of the dispersible tablet in children (aged 2 to 12 years) with idiopathic or familial PAH (Beghetti et al., 2009). The safety profile in these studies was consistent with that seen in the adult population.

BREATHE-3 evaluated use of bosentan (31.25, 62.5, or 125 mg twice daily for 12 weeks) in 19 children (<15 years of age) with PAH, 10 with concomitant Flolan use (Barst et al., 2003a). Pharmacokinetic and hemodynamic parameters were assessed in all subjects, and efficacy (6-min walk test and peak oxygen consumption) was assessed in the subset of children aged ≥ 8 years who were able to comply with the measures. Bosentan significantly improved key hemodynamic parameters and peak oxygen consumption, and was well tolerated (mean change from baseline for mPAP, -8 mm Hg ; PVR, $-300 \text{ dyne} \cdot \text{s/cm}^5$; both $P < 0.05$).

FUTURE-1 evaluated the new dispersible tablet formulation of bosentan in 36 children (aged 2 to 12 years) with idiopathic or familial PAH (Beghetti et al., 2009). The pediatric formulation was a clover-shaped dispersible tablet containing 32 mg bosentan quadrisectioned by score lines on one side, enabling it to be divided into four parts (each containing a dose of 8 mg). Patients initially received 2 mg/kg twice daily for 4 weeks followed by 4 mg/kg twice daily until week 12. In FUTURE-1, children had lower exposure to bosentan than adults but exposure similar to that of children who participated in BREATHE-3. Bosentan concentrations after doses of 2 and 4 mg/kg were similar. In addition, the safety and tolerability profile of bosentan was consistent with that observed in previous placebo-controlled clinical trials in the adult population. No cases of elevated liver enzymes or anemia were reported.

Additional uncontrolled studies have shown functional and hemodynamic benefit from long-term treatment with bosentan in children with PAH (Rosenzweig et al., 2005; Maiya et al., 2006; Ivy et al., 2010; Hislop et al., 2011), including as part of combination therapy (Beghetti, 2009) and with lower rates of liver function abnormalities (3%) compared with adolescents and adults (8%) (Beghetti et al., 2008).

d. Commercial considerations. In 2001, bosentan became the first oral PAH therapy and was available only through a special restricted distribution program in the United States because of the risk of liver injury and teratogenicity. As part of this program, patients are required to obtain monthly liver function and pregnancy tests. Treatment with bosentan consists of an initial dosage of 62.5 mg twice daily for 4 weeks, followed by a maintenance dose of 125 mg twice daily. The annual AWP cost in the United States is approximately \$78,000/year (Red Book, 2010). The patent for bosentan will expire in November 2015.

Bosentan is associated with risks that include liver injury (usually reversible), anemia, teratogenicity, and male sterility. Contraindications or limitations include patients with moderate or severe liver impairment (aminotransferase levels greater than 3 times normal), pregnancy, and breastfeeding. Venitz et al. (2011) have emphasized that bosentan is susceptible to multiple drug interactions, in part because of the dependence on multiple P450 pathways to form active circulating metabolites and known metabolic autoinduction. Use of hormonal contraception, lopinavir/ritonavir, cyclosporine, ketoconazole, warfarin, statins, tacrolimus, rifampin, and glyburide have potential for interactions as a result of the inhibition of transport protein-mediated uptake of bosentan into hepatocytes (rifampin, cyclosporine) or CYP450 interactions.

Because bosentan induces the CYP3A4 P450 hepatic enzymes involved in the metabolism of hormonal contraceptives (estradiol, progesterone), reduced efficacy of hormonal contraceptives may occur. This possibility is of

special concern given the high rate of maternal mortality (30–50%) with PAH in pregnancy (Lane and Trow, 2011) and significant risk of teratogenicity with bosentan (Pregnancy Class X). The bosentan label includes a warning that women of childbearing potential should not rely solely on hormonal contraception and should use two reliable forms of contraception during and for 1 month after stopping bosentan treatment (unless using a Copper T 380A intrauterine device or LNg 20 intrauterine system, in which case no other contraception is needed). Actelion was required by the FDA to conduct a postmarketing study in healthy volunteers to evaluate the potential metabolic interactions of combined bosentan and oral hormonal contraceptive use. The results of this study showed that bosentan decreased the plasma concentrations of combination norethisterone and ethinyl estradiol in healthy women (van Giersbergen et al., 2006), confirming concerns that patients with PAH treated with bosentan may have reduced efficacy of oral hormonal contraceptives.

Actelion was also required to conduct a small open-label postmarketing study evaluating the effect of bosentan on testicular function. Study results have not been published in a scientific journal but were described in a 2009 U.S. label revision, which summarized findings from an open-label study evaluating effects of 6 months of bosentan treatment on testicular function in 25 men with PAH and normal baseline sperm count. Twenty-three patients completed the study and two discontinued as a result of adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment. No changes in sperm morphology, sperm motility, or hormone levels were observed. After bosentan discontinuation, sperm count returned to normal range. One patient developed marked oligospermia (sperm count below 20 million/ml) at 3 months, and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. After bosentan was discontinued in this patient, the sperm count returned to baseline levels after 2 months.

e. Additional pulmonary arterial hypertension and pulmonary hypertension populations. The clinical trials supporting approval of bosentan were limited to patients with PAH that was either idiopathic or associated with connective tissue disease, and functional class III or IV status (study 351 and BREATHE-1). These patients typically are included in clinical trials because they show the greatest treatment effects. As described earlier, additional studies were conducted in patients with PAH and mild disease (EARLY trial) (Galié et al., 2008b), PAH related to HIV infection (Sitbon et al., 2004), and congenital heart disease (Galié et al., 2006), and pediatric populations (Barst et al., 2003a; Beghetti et al., 2009) to support various label expansions in the EU, Canada, and United States.

To investigate potential benefit in other patient populations with PAH and PH, additional trials have been conducted:

- Patients with PAH with functional class IV (severe) status who are receiving concomitant intravenous epoprostenol (BREATHE-2): completed.
- PH (group 3) associated with chronic obstructive pulmonary disease (COPD): completed.
- PH (group 4) as a result of chronic thromboembolic disease (BENEFIT): completed.
- PH associated with sickle cell disease (ASSET-1 and -2): completed.
- PH group 1 (PAH) patients receiving background sildenafil therapy (COMPASS-2): ongoing.
- PH group 1 (PAH) patients receiving sildenafil after suboptimal response to bosentan (COMPASS-3): completed.

BREATHE-2 was a randomized, double-blind, placebo-controlled trial that evaluated use of combined epoprostenol plus bosentan versus epoprostenol alone in adults with PAH (Humbert et al., 2004). Thirty-three subjects started receiving epoprostenol and were then randomized after 48 h in a two-to-one ratio to receive bosentan or placebo for 16 weeks. Doses of epoprostenol were started at $2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with titration up to $14 \pm 2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at week 16; bosentan dose was 62.5 mg twice daily for 4 weeks with an increase to 125 mg twice daily for 12 weeks. Combination epoprostenol and bosentan resulted in a nonsignificant ($P = 0.08$) decrease in total pulmonary resistance (primary endpoint) compared with epoprostenol use alone. There was no difference between groups in exercise capacity (6-min walk distance), although both groups experienced clinically meaningful improvements (median change from baseline of 68 m in the bosentan-epoprostenol group versus 74 m in the placebo-epoprostenol group). Four withdrawals occurred in the combined group (including two deaths), with one withdrawal in the epoprostenol group.

i. Pulmonary arterial hypertension associated with chronic obstructive pulmonary disease. Patients with parenchymal lung disease associated with hypoxia have been excluded from studies of PAH because of debate over concerns of lack of efficacy of vasodilator agents in COPD. Although treatment with pulmonary vasodilators in patients with PH related to COPD may improve mPAP by inhibition of hypoxic pulmonary vasoconstriction, this effect may also impair gas exchange by increasing perfusion in poorly ventilated lung units with low ventilation/perfusion ratios and lowering arterial partial pressure of oxygen (Melot et al., 1984; Valerio et al., 2009). Small, uncontrolled studies of some PAH therapies (e.g., sildenafil) in patients with PH associated with COPD have found benefit in exercise and hemodynamic parameters after 12 weeks of treatment (Alp et al., 2006). As a result, a double-blind, placebo-controlled

study was conducted to evaluate 30 patients with severe COPD who were randomly assigned in a two-to-one ratio to receive either bosentan or placebo for 12 weeks (Stolz et al., 2008). Compared with placebo, patients treated with bosentan showed no significant improvement in exercise capacity (6-min walk distance) and had deterioration of arterial oxygen pressure, the alveolar-arterial gradient, and quality of life. This finding is consistent with the symptoms of dyspnea and decreased exercise capacity in COPD due primarily to pulmonary parenchymal disease and not to PH. However, there is a small subset of patients with COPD in whom PH is believed to be disproportionate to the degree of airflow limitation. In these patients, PAH-specific therapy may be of value (Minai et al., 2010).

ii. *Pulmonary hypertension due to chronic thromboembolic disease (BENEFIT)*. A double-blind, randomized, placebo-controlled study evaluated 157 patients with either inoperable CTEPH or PH after pulmonary endarterectomy and where repeat surgery was not considered an appropriate therapeutic option (Jaïs et al., 2008). Bosentan significantly improved the placebo-corrected change from baseline to week 16 for cardiopulmonary hemodynamics (PVR, cardiac index) but not exercise capacity. A meta-analysis of eight single-arm cohort studies (175 patients), the aforementioned randomized double-blind study, one case-control study, and one case report showed a 35.9-m weighted mean increase in 6-min walk distance after 3 to 6 months of bosentan treatment in patients with CTEPH (9 studies, 208 patients) (Becattini et al., 2010).

iii. *Pulmonary hypertension associated with sickle cell disease (ASSET-1 and -2)*. Two randomized, double-blind, placebo-controlled, 16-week studies were initiated in patients with PAH (ASSET-1) and pulmonary venous hypertension (ASSET-2) associated with sickle cell disease. Both studies were stopped because of slow site initiation and patient enrollment ($n = 26$); 6-min walk distance data were not analyzed. In both studies, bosentan seemed to be well tolerated, and exploratory analyses showed nonsignificant improvements in cardiac output and PVR in the bosentan-treated patients compared with those receiving placebo (Barst et al., 2010).

f. *Additional study populations*. After positive results from an acute hemodynamic study of single-dose sildenafil added to established bosentan therapy (COMPASS-1) (Gruenig et al., 2009), studies in patients with PAH adding bosentan to background sildenafil therapy (COMPASS-2) or adding sildenafil after suboptimal response to bosentan (COMPASS-3) were initiated.

- COMPASS-2 (<http://clinicaltrials.gov> identifier NCT00303459) is a trial of 350 patients with PAH (aged 12 years or greater) to evaluate the benefits of adding 125 mg of bosentan twice daily or placebo for 16 weeks to background sildenafil therapy. Coprimary endpoints are time from baseline to first ad-

judicated morbidity/mortality event and change from baseline to week 16 in 6-min walk distance. Study completion is projected to occur in 2014.

- COMPASS-3 was an open-label trial of 100 patients with PAH (aged 12 years or greater) to evaluate the benefits of adding sildenafil in those with a suboptimal response from background bosentan therapy (Benza et al., 2010a). Patients received bosentan (125 mg twice daily) for 16 weeks and, on the basis of reaching a 6-min walk distance of at least 380 m, continued to receive either bosentan monotherapy or combination therapy (bosentan plus sildenafil 20 mg three times daily) for an additional 12 weeks. Baseline mean 6-min walk distance was 273 m. At week 16, 16 patients (16%) achieved a 6-min walk distance of 380 m. Of the remaining 84 patients, who received combination sildenafil plus bosentan, 15 (18% of those achieving an inadequate response from bosentan monotherapy) achieved a 6-min walk distance of 380 m at week 28. Mean improvement in 6-min walk distance was 22 m at week 16 and 45 m at week 28. Both treatment regimens were well tolerated.

5. Ambrisentan

a. *Clinical studies*. Ambrisentan (Letairis) is an oral selective ET_A -receptor antagonist (ET_A versus ET_B receptor >4000-fold) with an effective half-life of 9 h (Riechers et al., 1996; Letairis package insert, 2011). Ambrisentan is metabolized mainly by UDP glucuronosyltransferases 1A9S, 2B7S, and 1A3S and, to a lesser extent, by CYP3A and CYP2C19 (Letairis package insert, 2011; Venitz et al., 2011).

Ambrisentan was initially developed by Myogen (Westminster, CO) under license from Abbott (Abbott Park, IL). Myogen was subsequently acquired in 2006 by Gilead Sciences (Foster City, CA). Ambrisentan was then licensed to GlaxoSmithKline by Gilead Sciences for all regions outside of the United States.

In 2007, the FDA approved 5- and 10-mg ambrisentan for the once-daily treatment of patients with PH group 1 (PAH) and functional class II or III symptoms to improve exercise capacity and delay clinical worsening. Ambrisentan was subsequently approved for use in other regions, including Canada (2008), EU (2008), New Zealand (2009), Australia (2009), and Japan (2010) under the trade name Volibris.

Approval of ambrisentan was based on a small phase 2 trial and two larger phase 3 trials. The phase 2 study was a randomized, double-blind, dose-finding trial that evaluated 64 patients receiving 1.0, 2.5, 5.0, or 10 mg of ambrisentan once daily for 12 weeks (Galié et al., 2005a). Ambrisentan significantly improved 6-min walk distance (36.1 m, $P < 0.0001$) with similar increases for each dose group (range, 33.9–38.1 m). Improvements were also observed in Borg dyspnea index, functional class, mPAP (–5.2 mm Hg, $P < 0.0001$), and cardiac

index ($0.33 \text{ l} \cdot \text{min}/\text{m}^2$, $P < 0.0008$). The incidence of elevated liver enzymes greater than 3 times normal were observed in two patients (3.1%) receiving the 5-mg dose.

The two pivotal phase 3 trials were identical in design (except for overlapping doses) and conducted concurrently in different geographic regions. ARIES-1 (North America, Australia) enrolled 202 patients who received 5 or 10 mg of ambrisentan or placebo taken once daily for 12 weeks. ARIES-2 (Western/Eastern Europe, South America, Israel) enrolled 192 patients who received 2.5 or 5 mg of ambrisentan or placebo taken once daily for 12 weeks.

Figure 8 shows results of 6-min walk distances in ARIES-1 and -2. In ARIES-1, the (placebo-corrected) mean 6-min walk distance improved by 31 m for 5 mg of ambrisentan ($P = 0.008$) and 51 m for 10 mg of ambrisentan ($P < 0.001$) (Galié et al., 2008a). In ARIES-2, the mean (placebo-corrected) 6-min walk distance im-

proved by 32 m for 2.5 mg of ambrisentan ($P = 0.02$) and 59 m for 5 mg of ambrisentan ($P < 0.001$) (Galié et al., 2008a).

Ambrisentan significantly improved time to clinical worsening in ARIES-2 but not ARIES-1. However, a significant improvement in time to clinical worsening was observed when data from the 5-mg groups in both ARIES-1 and -2 were combined ($P = 0.005$). The combined analysis of the 5-mg groups also showed that ambrisentan significantly improved other secondary efficacy endpoints, including functional class, several SF-36 Health Survey subscales (quality of life), and Borg dyspnea index ($P < 0.05$).

Ambrisentan was well tolerated in both trials, headache being the most frequent adverse event. The integrated analysis showed that no patient treated with ambrisentan developed serum aminotransferase concentrations greater than 3 times the normal range at any time during the 12-week treatment period, compared with three patients in the placebo group (2.3%).

Oudiz et al. (2009) evaluated 383 patients who participated in the pivotal ARIES-1 and -2 trials and a long-term extension phase (ARIES-E). The first 24 weeks of the ARIES-E study was a blinded, fixed-dose period; after 24 weeks, the randomized treatment assignment remained blinded but dose adjustments were permitted per investigator discretion. After 2 years of treatment, the mean change from baseline in 6-min walk distance was improved for the 5-mg (23 m; 95% CI, 9–38 m) and 10-mg (28 m; 95% CI, 11–45 m) groups but not the 2.5-mg (7 m; 95% CI, –13 to 27 m) group. Estimates of survival for the combined dose group were 94% at 1 year and 88% at 2 years. No new safety signals were observed, and the annualized risk of aminotransferase abnormalities greater than 3 times normal was approximately 2% per year.

A subsequent long-term, single-arm open-label study (ARIES-3) evaluated treatment with 5 mg of ambrisentan daily for 6 months in a diverse population of 224 patients that included some patients with non-group 1 PH (such as CTEPH or PH owing to lung diseases) and use of background PAH therapy (Badesch et al., 2012). Consistent with ARIES-1 and -2, ambrisentan improved exercise capacity (6-min walk distance change from baseline, 21 m; $P < 0.001$) with no new safety signals. Increases in 6-min walk distance were observed for all PH subtypes other than 45 patients with PH group 3 (PH associated with lung disease). In addition, consistent with other PAH trials, patients receiving ambrisentan monotherapy had greater treatment effects compared with those receiving background therapy.

Ambrisentan was initially assumed to have ERA class effects of liver injury, teratogenicity, testicular injury, reduced male fertility, and anemia. As a result, monthly laboratory monitoring for liver injury and pregnancy was required through a special restricted distribution program at time of approval to obtain drug in the United

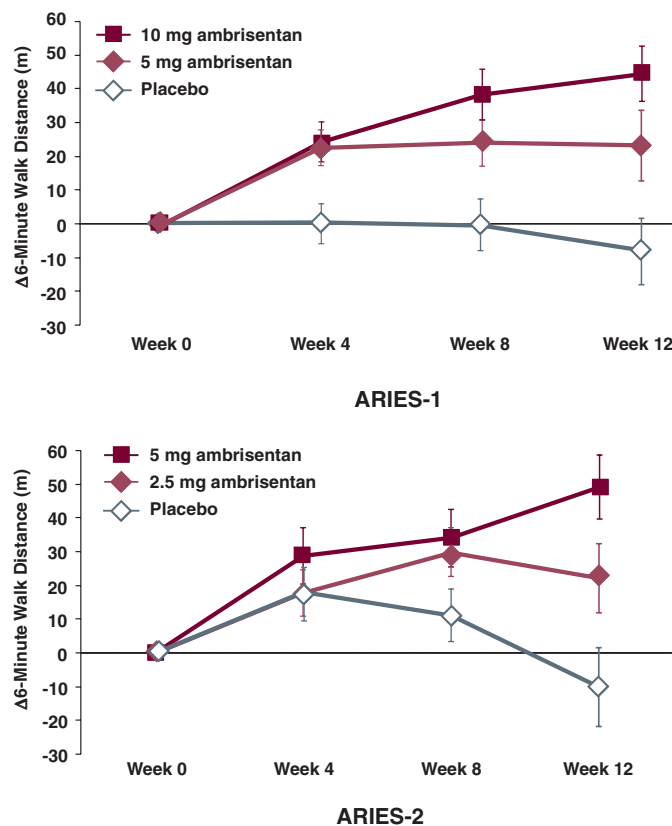


FIG. 8. Mean (\pm S.E.) change from baseline to week 12 in the 6-min walk distance for placebo and ambrisentan groups of ARIES-1 and ARIES-2. For ARIES-1: $P = 0.008$, 5 mg of ambrisentan once daily versus placebo; $P < 0.001$, 10 mg of ambrisentan once daily versus placebo. For ARIES-2: $P = 0.022$, 2.5 mg of ambrisentan once daily versus placebo; $P < 0.001$, 5 mg of ambrisentan once daily versus placebo. A total of 201 patients in ARIES-1 and 192 patients in ARIES-2 were included in these intention-to-treat analyses. [Reprinted from Galié N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, et al. (2008) Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 117:3010–3019. Copyright © 2008 American Heart Association. Used with permission.]

States. In 2011, the FDA removed the warning label for liver injury (and requirement for monthly liver function testing) for ambrisentan on the basis of postmarketing data involving more than 7800 patient years. These data confirmed the absence of meaningful differences in liver function abnormalities between patients receiving ambrisentan and placebo observed in the ambrisentan pivotal clinical trials. The mechanism by which ERAs induce liver toxicity is unclear; however, preclinical data suggest that bosentan may increase serum aminotransferase levels by inhibiting hepatocyte bile salt excretion and uncoupling of lipid-bile salt secretion, resulting in alterations of bile composition (Fattinger et al., 2001). In contrast, ambrisentan does not affect the bile salt export pump (Frampton 2011).

b. Commercial considerations. The possibility of greater benefits from selective ET_A-receptor antagonism (compared with the dual ET_A/ET_B antagonism of bosentan) has been raised but remains speculative (Opitz et al., 2008). Bosentan data in PAH are robust, diverse, and have been collected in a large number of patients. However, ambrisentan has several key features that are important (compared with bosentan): 1) FDA removal of the warning label for liver injury and requirement for monthly liver function testing; 2) once-daily dosing compared with twice-daily dosing with bosentan; 3) dose flexibility with two approved efficacious doses (5 and 10 mg); and 4) only one drug interaction that is considered clinically relevant (cyclosporine A) (Letairis package insert, 2011; Venitz et al., 2011).

Clinicians have observed that some patients who do not respond to a specific ERA (or who have elevation of liver enzymes while receiving therapy) may do well when receiving a different ERA (McGoon et al., 2009; Zacà et al., 2009; Eriksson et al., 2011). This feature could allow ambrisentan to gain additional market share, especially given the 2011 removal of the U.S. warning label related to liver injury. The annual U.S. cost of ambrisentan is similar to that of bosentan (AWP approximately \$78,000/year; Red Book, 2010). The patent for ambrisentan for the treatment of PAH will expire in 2015.

Unlike bosentan, ambrisentan does not interact with either tadalafil or sildenafil (Spence et al., 2008, 2009). As a result, a 33-patient open-label trial (ATHENA-1) was conducted to evaluate whether the addition of 24 weeks of ambrisentan will improve PVR (primary endpoint) in patients with PAH who have a suboptimal response with PDE-5 inhibitor monotherapy (Oudiz et al., 2011). Patients received 5 mg of ambrisentan once daily for 4 weeks with an increase to 10 mg once daily for the remaining 20 weeks. Significant and clinically meaningful improvements were observed for 6-min walk distance (18 m; $P = 0.0437$), hemodynamics (PVR, -249 dyne \cdot s/cm⁵; $P < 0.0001$), and a plasma biomarker of heart failure. Gilead and GlaxoSmithKline are sponsoring a multinational study that began in 2010. This study

(AMBITION), which has time to clinical failure as the primary outcome measure, is enrolling treatment-naïve patients with PAH to receive either a combination of tadalafil and ambrisentan or monotherapy with either of the drugs (<http://clinicaltrials.gov> identifier NCT01178073). The year of expected study completion is 2013.

6. Sitaxentan

a. Withdrawn from market. In December 2010, Pfizer voluntarily withdrew the oral selective ET_A-receptor antagonist sitaxentan (Thelin) from the market and stopped clinical development for PAH as a result of concerns about irreversible liver damage that could not be predicted with monthly liver function enzyme monitoring (Galié et al., 2011; Lee et al., 2011). Patients receiving concomitant sitaxentan (name later changed to sitaxentan) and warfarin also required various significant decreases in warfarin dose to prevent supratherapeutic international normalized ratio levels and increased risk of bleeding (Barst 2007). Sitaxentan had been sold in the EU, Canada, and Australia.

7. Nitric oxide

a. Mechanism of action. Nitric oxide is a potent vasodilator, and local NO production in the lung, via production of cGMP and intracellular calcium signaling, regulates pulmonary perfusion depending on alveolar ventilation. Inhaled NO can be rapidly and selectively delivered to the pulmonary vasculature (Steinhorn 2008). PPHN, a subtype of group 1 PAH, is characterized by marked PH that causes right-to-left extrapulmonary shunting of blood across a patent foramen ovale and ductus arteriosus and causes hypoxemia.

b. Clinical studies. Nitric oxide (INO_{max}) for inhalation was developed by INO Therapeutics (Clinton, New Jersey). On the basis of randomized controlled trials, NO was approved by the FDA in 1999 for term and near-term (>34 weeks) neonates with PPHN (Macrae et al., 2004). In 2001, approval was obtained in the EU. In 2007, Ikaria (Clinton, NJ) acquired INO Therapeutics.

The recommended dose of INO_{max} is 20 ppm, maintained for up to 14 days or until the underlying systemic oxygen desaturation has resolved. Concerns with long-term NO therapy include rebound PH after stopping therapy and development of methemoglobinemia (Ichnose et al., 2004).

Initial approval was based on two large randomized, controlled pivotal trials evaluating use of NO in 483 neonates requiring assisted ventilation, and with hypoxemic respiratory failure (oxygenation index ≥ 25) and PH (Neonatal Inhaled Nitric Oxide Study Group, 1997; Clark et al., 2000). A third trial, which provided supportive data, was terminated early as a result of poor enrollment on the basis of perceived efficacy in the two earlier trials (Davidson et al., 1998).

NO significantly reduced the need for extracorporeal membrane oxygenation support by approximately 40% at 30 days (Clark et al., 2000) and 27% at 120 days (Neonatal Inhaled Nitric Oxide Study Group, 1997). NO

was not associated with toxicity but did not reduce mortality, length of hospitalization, or the risk of neurodevelopmental impairment.

In 2011, the FDA granted INO_{\max} an additional 6 months of patent protection (until July 2013) on the basis of data submitted from clinical trials of INO_{\max} in preterm infants at risk for bronchopulmonary dysplasia. In 2011, the EU label was expanded to include treatment of PH in patients of all ages during and after heart surgery. Small, controlled studies have shown that inhaled NO alone or in combination with other vasodilators improves hemodynamic indices in patients with PH after cardiac surgery (Schmid et al., 1999; Fernandes et al., 2011; Matamis et al., 2012).

A phase 2 double-blind randomized trial evaluating the safety and efficacy of 16 weeks of inhaled NO (versus placebo) as add-on therapy in symptomatic adults with PAH is in progress (<http://clinicaltrials.gov> identifier NCT01457781).

8. Sildenafil

a. Mechanism of action. NO is a potent vasodilator and, to a lesser extent, inhibitor of platelet activation and vascular smooth-muscle cell proliferation. PAH is associated with impaired release of NO (and thus excessive vasoconstriction, vascular proliferation, and thrombi) as a result of little or no expression of NO synthase in the vascular endothelium of pulmonary arteries (Giaid and Saleh, 1995).

PDE-5 is the main phosphodiesterase in lung and present in large amounts (Corbin et al., 2005); inhibiting PDE-5 maintains high cGMP levels, which promote vasodilatory (Napoli and Ignarro, 2003; Francis et al., 2010), antiproliferative (Tantini et al., 2005; Wharton et al., 2005), and antiplatelet (Gresele et al., 2011) effects of endogenous NO. In addition, although application to humans remains untested, preclinical data suggest that sildenafil—and PDE-5 inhibition in general—may also increase intracellular calcium and contractility in hypertrophied myocardium and be of special benefit to patients with ventricular dysfunction (Nagayama et al., 2009; Zhang et al., 2010; Xie et al., 2012).

b. Clinical studies. Sildenafil is the oral PDE-5 inhibitor initially marketed by Pfizer (New York, NY) for erectile dysfunction worldwide under the trade name Viagra. Sildenafil and its active metabolite have a terminal half-life of approximately 4 h and are cleared mainly by CYP3A4 (major) and CYP2C9 (minor). After priority review, sildenafil was approved for PAH by the FDA and EMA in 2005 with the trade name Revatio.

The initial approval in the United States of sildenafil at 20 mg three times daily for the treatment of patients with PH group 1 (PAH) was to improve exercise ability, regardless of functional class or etiology. The EU label is restricted to patients with PAH and the predominant functional class status observed in the pivotal study (functional class II and III).

The main regulatory submission for sildenafil was based on results from a single pivotal trial, SUPER-1 (Galié et al., 2005b). SUPER-1 was a multicenter, double-blind, randomized study that evaluated the effects of oral sildenafil 20 mg ($n = 69$), 40 mg ($n = 67$), or 80 mg ($n = 71$) three times daily compared with placebo ($n = 70$) for 12 weeks in 278 adults with PAH that was idiopathic or associated with connective tissue disease or congenital shunts (repaired at least 5 years earlier). The study was conducted at 60 centers throughout North America, Europe, and Asia. SUPER-1 allowed background therapy with anticoagulants, digoxin, calcium channel blockers, diuretics, and oxygen. Treatment with ERAs or prostanoids was prohibited.

The primary efficacy endpoint was change in 6-min walk distance from baseline to week 12. Secondary endpoints were Borg dyspnea score, functional class, time to clinical worsening, cardiopulmonary hemodynamics, and safety. Clinical worsening was defined as death, transplantation, hospitalization for PAH, or initiation of additional therapies for PAH such as epoprostenol or bosentan. Randomization to treatment groups was stratified for baseline walking distance (<325 or ≥ 325 m) and type of PAH (idiopathic/familial versus associated with other conditions).

Of 360 patients screened, 277 were treated. All groups were well balanced for baseline demographic and other characteristics. Most subjects had idiopathic or heritable PAH (63%) and moderate functional class (III) symptoms (58%). Twelve patients discontinued the study with no significant differences between treatment groups (2 in placebo, 2 in 20 mg, 3 in 40 mg, and 5 in 80 mg). The most common reason for discontinuation was hospitalization for worsening PAH.

Each sildenafil dose group, compared with placebo, significantly improved 6-min walk distance over 12 weeks (Fig. 9). The placebo-adjusted change in 6-min walk distance ranged from 45 to 50 m, with no significant evidence of dose-effect on the primary endpoint (6-min walk distance). Benefit in exercise capacity also occurred as early as the initial time assessed for all doses (4 weeks), and was maximal at end of study (week 12). Each sildenafil dose group, compared with placebo, also significantly improved key hemodynamic parameters such as mPAP and PVR (in a marked dose-dependent manner). This latter finding raises the possibility that the lack of dose-response observed with the improved exercise capacity (6-min walk distance) may be due to mechanisms other than improved cardiac output per se. An alternate explanation is that a true dose-response for exercise capacity existed at the doses studied but required a longer period of observation than 12 weeks or an increased sample size to detect; in the longer (16-week) tadalafil trial in PAH, the greatest separation in exercise capacity among the three highest dose groups occurred between weeks 12 and 16 (Galié et al., 2009a).

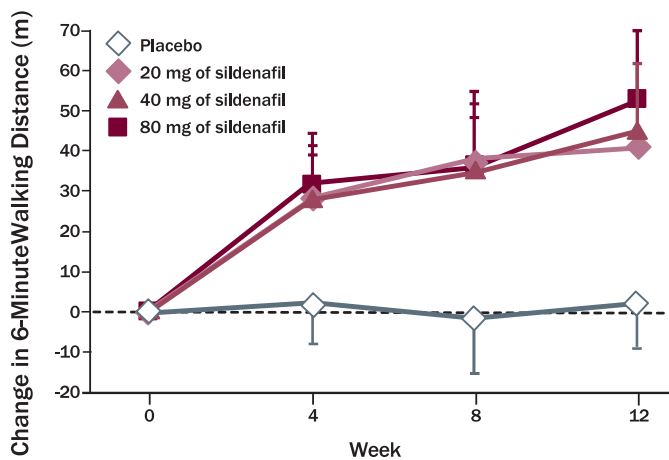


FIG. 9. Mean changes from baseline, with 95% confidence intervals, in the 6-min walk distance at week 12 in the placebo and sildenafil groups ($P < 0.001$ for the comparison of sildenafil in doses of 20, 40, and 80 mg three times daily with placebo). In this intention-to-treat analysis, 266 (of 277 treated) patients for whom outcome data were available were included. [Reprinted from Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, et al. (2005) Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 353:2148–2157. Copyright © 2005 Massachusetts Medical Society. Used with permission.]

Sildenafil (each dose), compared with placebo, also significantly improved functional class at week 12, using the criterion of improvement of at least one functional class. Sildenafil did not improve time to (or incidence of) clinical worsening or change from baseline in scores on the Borg dyspnea scale.

The most common adverse events (in order of frequency and pooling of sildenafil groups) were headache (46% sildenafil versus 39% placebo), flushing (12 versus 4%), dyspepsia (12 versus 7%), and back pain (12 versus 11%). The only adverse event with a statistically significant difference between pooled sildenafil and placebo groups was epistaxis (7 versus 1%).

Retinal hemorrhages were more common with sildenafil treatment compared with placebo treatment (2% pooled sildenafil versus 0% placebo). This finding, coupled with the increased incidence of epistaxis in sildenafil-treated patients, raised concerns that PDE-5 inhibition could increase bleeding in patients with PAH. The most likely mechanism for this effect could be PDE-5-induced decreased platelet aggregation coupled with anticoagulation from warfarin, the most common drug used by patients with PAH.

The relationship between PDE-5 inhibition and the severe visual condition of nonarteritic anterior ischemic optic neuropathy (NAION) is unclear; an association has been raised because of the occurrence of extremely rare cases of NAION in the postmarketing setting of PDE-5 inhibitors in patients with erectile dysfunction (estimated incidence of 2.8 cases per 100,000 patient-years of sildenafil exposure) (Gorkin et al., 2006). No cases of NAION or visual impairment occurred during SUPER-1 or in the SUPER-2 extension trial (with most patients taking 80 mg three times daily per protocol for 3 years).

c. Long-term follow-up. Of 277 patients treated in the 12-week, randomized, double-blind study (SUPER-1), 257 completed the trial and entered an open-label, uncontrolled extension phase (SUPER-2) (Rubin et al., 2011a). Patients randomized to sildenafil 80 mg three times daily in SUPER-1 continued to receive the same dose in SUPER-2; those randomized to 20 mg, 40 mg, or placebo three times daily in SUPER-1 were titrated to 80 mg three times daily in SUPER-2. If a patient deteriorated, additional approved PAH therapy (including ERA or prostacyclin analog) could be started during SUPER-2. The median duration of sildenafil treatment across SUPER-1 and -2 was 1242 days (range, 1–1523 days); 170 of 277 patients (61%) completed both studies. Of 104 patients who did not complete SUPER-2, 59 died and an additional 45 discontinued, mainly as a result of adverse events that were not considered to be treatment-related. After 3 years, most patients (60%) improved or maintained their functional status noted at the time of SUPER-1 entry, and 46% maintained or improved their 6-min walk distance. Three-year estimated survival was 79% and no deaths were considered to be treatment-related.

d. Label expansion.

i. Delay in clinical worsening. In 2009, the FDA expanded the claims of benefit to include delay of clinical worsening on the basis of data from the large, multinational placebo-controlled study of sildenafil added to background epoprostenol therapy (PACES-1 trial) (Simonneau et al., 2008). This study evaluated 267 patients with PAH randomly assigned to receive either 16 weeks of sildenafil (20 mg three times daily titrated to 80 mg three times daily at 4-week intervals) or placebo added to background epoprostenol therapy. Of 265 patients who received treatment, 256 (97%) patients (123 in the placebo group and 133 in the sildenafil group) completed the study. Sildenafil (compared with placebo) significantly improved 6-min walk distance at week 16 (mean placebo-adjusted change from baseline, 28.8 m; $P < 0.001$). In addition, sildenafil significantly improved mPAP compared with those receiving placebo (mean placebo-corrected treatment effect, -3.9 mm Hg; $P = 0.002$). Patients receiving sildenafil also experienced a significant improvement in time to clinical worsening versus placebo ($P < 0.001$). Although mortality was not a prespecified endpoint, 7 patients died during the 16 week study—all receiving placebo. Adverse events that were more common in patients treated with sildenafil who were receiving combined therapy (compared with those receiving epoprostenol monotherapy) included headache (57 versus 34%), dyspepsia (16 versus 2%), pain in extremity (25 versus 18%), and nausea (25 versus 18%).

ii. Intravenous formulation. In 2009, the FDA approved an intravenous form of sildenafil (Revatio) given as a bolus injection (10 mg three times a day) for patients unable to take the oral formulation. Subsequent

approvals have occurred in the EU and other regions. A 10-mg sildenafil intravenous bolus provides acute exposure, tolerability, and safety similar to that provided by the oral 20-mg tablet (Vachieri et al., 2011).

iii. Pediatrics. In May 2010, sildenafil became the first PAH-specific drug approved for children with PAH (aged 1–17 years) after approval in the EU for use as an oral suspension or tablet. This approval was based on a placebo-controlled study that evaluated 235 patients aged 1 to 17 years (≥ 8 kg) with idiopathic/familial PAH or PAH associated with congenital heart disease randomized to receive one of four treatments: low-, medium-, or high-dose sildenafil versus placebo three times daily for 16 weeks (Barst et al., 2012). The actual sildenafil doses ranged between 10 and 80 mg and were based on the patient's weight. The primary outcome measure was percentage change in peak oxygen consumption by cycle ergometry for the combined sildenafil groups (versus placebo) in children who were able to exercise reliably. Cardiopulmonary hemodynamics were assessed in all patients as secondary endpoints. Of 234 treated patients, 106 patients (45%) were ≥ 7 years of age and developmentally able to perform the cycle ergometry reliably. Sildenafil treatment (combined dose groups versus placebo) resulted in a marginally significant increase in oxygen consumption by cycle ergometry (placebo-adjusted change of 7.7%; $P = 0.056$). Efficacy was demonstrated with both the medium- and high-dose groups (versus placebo); the low dose was ineffective. There were no treatment-emergent deaths, and sildenafil was generally well tolerated.

The recommended dose of sildenafil in pediatric patients with PAH is 10 mg three times daily for those weighing 20 kg or less and 20 mg three times daily for those greater than 20 kg (Revatio EMA Summary of Product Characteristics). A long-term open-label extension trial allowed patients who had been receiving sildenafil monotherapy in the aforementioned placebo-controlled trial to continue with their randomized dose in the extension phase (until the last patient completed the 16-week controlled study); patients who received placebo in the controlled trial were randomized (in a blinded fashion) to low-, medium-, and high-dose sildenafil groups in the extension phase. More deaths occurred among patients randomized to the high-dose compared with lower dose groups, with the increased risk appearing after 2 years of treatment using sildenafil doses (i.e., 40–80 mg three times daily) higher than recommended in the Summary of Product Characteristics (Pfizer Direct Healthcare Professional Communication, 2011; Barst et al., 2012). Most deaths, which were more frequent in children with idiopathic or heritable PAH and increased baseline disease severity, were assessed by the investigators as being due to progression of PAH. Although up- or down-titrations were allowed in the extension study, the increased mortality was associated with the initial randomized (high) dose, regardless

of what dose the subject was receiving at death. Whether similar results would occur with use of sildenafil as part of combination therapy is unknown; add-on PAH-therapy was not allowed in the extension study.

iv. Additional pediatric populations. Intravenous sildenafil, approved only for adults who can not tolerate the oral formulation, has been used in the treatment of PPHN and in children with postoperative PH. In 36 neonates with a mean age of 34 h and persistent PH (29 receiving concomitant inhaled NO), intravenous sildenafil by continuous infusion for at least 48 h and up to 7 days resulted in acute and sustained improvement in oxygenation (Steinhorn et al., 2009), with survival of 35 neonates at day 28. Intravenous sildenafil given for a minimum of 24 h, compared with placebo, also reduced mPAP and shortened time to extubation for immediate postoperative PH in a study of 17 children (median age, 5 months) with congenital heart disease (Fraisie et al., 2011). Another study showed that intravenous sildenafil augmented the pulmonary vasodilator effect of inhaled NO in 15 infants after cardiac surgery, but produced systemic hypotension and impaired oxygenation (Stocker et al., 2003). In countries in which intravenous sildenafil was not available, intragastric sildenafil compared with placebo given to seven neonates with persistent PH and less than 3 days old (Baquero et al., 2006) and 31 full-term neonates with persistent PH (Vargas-Origel et al., 2010) improved oxygenation and survival.

e. Commercial considerations. Sildenafil represents a first-in-class drug that is orally administered, effective, and seemed to be safer than other PAH therapies at time of approval. Pharmacoeconomic evaluations of PAH therapies (excluding tadalafil) have concluded that sildenafil is the most cost-effective treatment for PAH on the basis of low price and net increase in quality of life (Garin et al., 2009; Strange et al., 2011). The annual AWP cost of Revatio in the United States is approximately \$18,500 (Red Book, 2010). The patents for sildenafil use in PAH are expected to expire in 2012 for the tablet formulation and in 2013 for the intravenous formulation.

A theoretical concern with sildenafil is its short half-life requiring three times daily administration for PAH and potential for wearing-off effects at the end of dosing periods. Although untested, the once-daily PDE-5 inhibitor tadalafil may have advantages in both convenience of dosing and a more sustained period of efficacy through the dosing period. Alternatively, observations from use of PDE-5 inhibitors for erectile dysfunction suggest that intracellular binding of drug and affinity to PDE-5 could be determinants of duration of therapeutic response as important as half-life per se (Dunn et al., 2007).

The efficacy of sildenafil for PAH has not been evaluated in patients receiving concomitant bosentan therapy (Revatio package insert, 2005). A July 2006 revision added language to the effect that in healthy subjects, coadministration of 125 mg of bosentan twice daily and

80 mg of sildenafil three times daily resulted in a 63% decrease in plasma concentration of sildenafil and a 50% increase in plasma concentration of bosentan (Burgess et al., 2008). A similar pharmacokinetic phenomenon has been reported with the coadministration of tadalafil and bosentan to healthy male subjects (Wrishko et al., 2008). This raises the possibility that higher doses of sildenafil—and PDE-5 inhibitors in general—might be needed for patients receiving concomitant sildenafil and bosentan treatment. This issue has not yet been addressed in clinical trials.

In 2009, the U.S. National Heart, Lung, and Blood Institute and Pfizer sponsored a 16-week study (Walk-PHaSST) to evaluate the effects of sildenafil in patients with PH associated with sickle cell anemia (Machado et al., 2011). The trial was prematurely stopped after 74 patients were randomized as a result of a higher percentage of subjects experiencing serious adverse events in the sildenafil arm (45% sildenafil versus 22% of placebo, $P = 0.022$). Subject hospitalization for pain related to sickle cell crisis was the predominant cause for this difference. Although the cause of this finding is unclear, it is possible that the myalgia and back pain known to occur with sildenafil could have contributed to the overall increase in pain (Machado et al., 2011). There was no evidence of a treatment effect on 6-min walk distance.

Additional small studies of sildenafil are being conducted in patients with PH associated with thalassemia (<http://clinicaltrials.gov> identifier NCT00872170) and PAH associated with HIV infection (<http://clinicaltrials.gov> identifier NCT00327080).

9. Tadalafil

a. Clinical studies. Lilly ICOS was a joint venture of ICOS Corporation (Bothell, WA) and Eli Lilly and Company (Indianapolis, IN). Tadalafil is the oral PDE-5 inhibitor initially developed and marketed worldwide by Lilly ICOS for erectile dysfunction under the trade name Cialis. Tadalafil was subsequently developed for PAH. In 2008, Eli Lilly, then the sole owner of tadalafil, sold the U.S. and Puerto Rico rights to market tadalafil for PAH to United Therapeutics. In late 2009, Nippon Shinyaku (Kyoto, Japan) signed a license agreement with Eli Lilly for sole marketing rights to tadalafil for PAH in Japan.

Tadalafil (Adcirca) was initially approved by the FDA in 2009 and subsequently in the EU (2009), Canada (2010), and Japan (2010) as an oral once-daily therapy (40 mg) to improve exercise ability in patients with PAH (WHO group 1). The EU label specifies the predominant functional class of the study population: II (mild) and III (moderate).

Similar to sildenafil, regulatory approval for PAH was based on results from a single pivotal trial (PHIRST) (Galié et al., 2009a). PHIRST was a multicenter, double-blind, randomized study that enrolled 405 patients who were either treatment-naïve or receiving background bosentan therapy. Patients were stratified by use of

bosentan therapy, 6-min walk distance (<325 m, >325 m), and type of PAH (idiopathic/familial versus other) to receive 2.5 mg ($n = 82$), 10 mg ($n = 80$), 20 mg ($n = 82$), or 40 mg ($n = 79$) of tadalafil or placebo ($n = 82$) once daily for 16 weeks. The study was conducted at 84 centers throughout North America, Europe, and Japan. Entry criteria were age ≥ 12 years with WHO functional class I to IV status and PAH that was idiopathic/familial or associated with anorexigen use, HIV infection, connective tissue disease, or congenital heart disease. A baseline 6-min walk distance between 150 and 450 m was also required. Treatment with epoprostenol, iloprost, or treprostinil was prohibited. Patients taking a maximal stable dose of 125 mg of bosentan twice daily for a minimum of 12 weeks before screening continued to receive bosentan in addition to the study drug during the trial.

The primary efficacy endpoint was change in 6-min walk distance from baseline to week 16. Secondary endpoints were change in Borg dyspnea score, WHO functional class, time to clinical worsening, quality of life (using the EuroQol and SF-36 scales), and (in a subset of patients) cardiopulmonary hemodynamics. Clinical worsening was defined as death, lung or heart transplantation, atrial septostomy, hospitalization for worsening PAH, worsening functional class, or initiation of new PAH-approved therapy.

Of 457 patients screened, 405 were treated. All groups were well balanced for baseline demographic and other characteristics. Most subjects had idiopathic/familial PAH (78%) and functional class II or III symptoms (97%); 53% of patients were receiving background bosentan therapy.

Ten, 20, and 40 mg of tadalafil (but not 2.5 mg) significantly improved 6-min walk distance over 16 weeks in a dose-dependent manner (Fig. 10). The placebo-adjusted change in 6-min walk distance ranged from 20 m (10-mg group) to 33 m (40-mg group). For the group receiving 40 mg, the placebo-adjusted change was 44 m ($n = 37$, $P < 0.01$) for treatment-naïve patients and 23 m ($n = 39$, $P = 0.09$) for patients receiving background bosentan (Galié et al., 2009a).

Compared with placebo, 20 and 40 mg of tadalafil significantly improved key hemodynamic parameters, including mPAP and PVR. Overall, patients who were treatment-naïve had a greater placebo-corrected treatment effect than patients receiving background bosentan therapy.

Forty milligrams of tadalafil also significantly improved both time to and incidence of clinical worsening compared with placebo ($P < 0.05$). Reduced hospitalization and improved WHO functional class were the main reasons for improved clinical worsening rates in the 40-mg tadalafil group. Compared with placebo, 40 mg of tadalafil significantly improved quality of life as reflected by six of the eight domains of the SF 36-health survey (all $P < 0.01$) and all sections of the EuroQol-5D

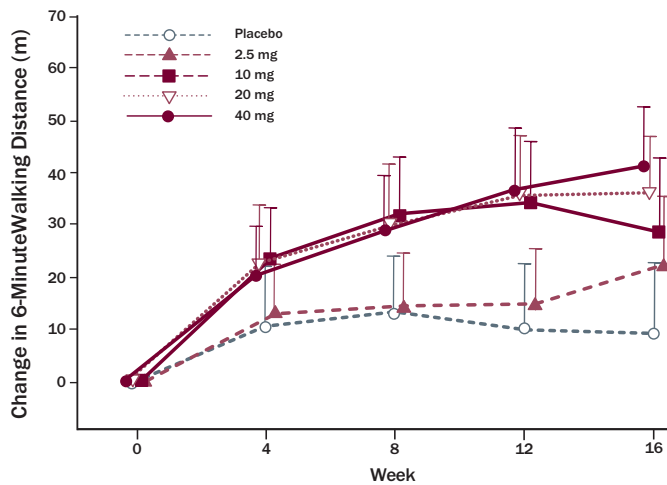


FIG. 10. Mean changes from baseline, with 95% percent confidence intervals, in the 6-min walk distance at week 16 in the tadalafil and placebo groups. Comparison of tadalafil with placebo for 2.5- ($P = 0.402$), 10- ($P = 0.047$), 20- ($P = 0.028$), and 40-mg ($P < 0.001$) once daily groups. In this intention-to-treat analysis, 392 (of 405 treated) patients for whom outcome data were available were included in descriptive statistics. [Reprinted from Galié N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, et al. (2009) Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 119: 2894–2903. Copyright © 2009 American Heart Association. Used with permission.]

questionnaire (all $P < 0.02$) from baseline to week 16. There were no significant differences between tadalafil and placebo groups for proportion of patients with improved WHO functional class or change from baseline in scores on the Borg dyspnea scale.

All doses of tadalafil were generally well tolerated, the most common adverse events being headache (32% pooled tadalafil versus 15% placebo), diarrhea (11 versus 11%), and flushing (9 versus 6%). Three deaths occurred during the 16-week study; one patient in the placebo group died because of PAH progression, one patient in the 10-mg tadalafil group died suddenly (unknown cause), and one patient in the 20-mg tadalafil group died as a result of histiocytosis hematophagic syndrome. Adverse events were not significantly different in the treatment-naïve patients compared with the patients receiving background bosentan. No instances of retinal hemorrhages or NAION were reported during the study.

b. Long-term follow-up. All patients who completed the 16-week, double-blind study (or who discontinued because of clinical worsening and were not receiving 40 mg of tadalafil) were eligible for a long-term extension study. Patients in the extension study received either 20 mg (those who received this dose during the 16-week study) or 40 mg (all other groups) of tadalafil in a blinded fashion.

Of 341 patients who completed the randomized 16-week study, 334 entered the extension study. In addition, 23 patients who prematurely discontinued the placebo-controlled study because of clinical worsening also entered the extension study. As of October 2007, 213 of

357 patients (60%) enrolled in the extension study had received tadalafil for at least 10 months. After 16 weeks of treatment, the mean change from baseline in the 6-min walking distance for these patients was 37 m (95% CI, 30–44); after 44 weeks, the mean change was 38 m (95% CI, 29–47) (Galié et al., 2009a).

c. Commercial considerations. Tadalafil is the second drug in its class to be approved for PAH (at a dose of 40 mg once daily). As with sildenafil, tadalafil is orally administered, effective, and seems to be safer than other classes of PAH therapies. Tadalafil is also metabolized predominantly by CYP3A.

In contrast to sildenafil, tadalafil has a long half-life (35 h) in patients with PAH, which allows once-daily administration (Adcirca package insert, 2009). Tadalafil has also shown benefit in patients with PAH receiving concomitant bosentan (Galié et al., 2009a; Barst et al., 2011b); sildenafil has not been studied in patients receiving concomitant bosentan in randomized, controlled trials (Galié et al., 2005b). Although comparator studies have not been done, the safety and efficacy profiles of tadalafil and sildenafil seem similar. The pivotal tadalafil trial showed that patients receiving 40 mg (without background bosentan) had a placebo-adjusted 6-min walk distance increase of 44 m at 16 weeks (Galié et al., 2009a); in a similarly designed trial, 20 to 80 mg of sildenafil for 12 weeks resulted in comparable placebo-adjusted 6-min walk distance improvement (40–50 m) (Galié et al., 2005b). In contrast to the 12-week pivotal sildenafil trial, the tadalafil trial was longer (16 weeks). This feature probably increased the ability to show a dose response, observe a benefit in clinical worsening, and collect long-term extension data on the optimal (approved) dose.

Tadalafil has not been studied in controlled trials of children with PAH. A retrospective review of 33 children with PAH (median age, 10 years; range, 4–18 years) of various causes showed that tadalafil was safe and seemed to reduce disease progression (Takatsuki et al., 2012). In this cohort, tadalafil was used as either initial therapy or initial PDE-5 inhibitor therapy added to background therapy in four children; the remaining 29 children—most receiving triple PAH-specific therapy—received tadalafil after transition from sildenafil, mainly for convenience of once-daily dosing.

The annual U.S. cost (AWP) of tadalafil (Adcirca) is approximately \$14,160 (Red Book, 2010). The patent for Adcirca for the treatment of PAH will expire in 2017.

III. Drugs in Late-Stage Development

A. Tyrosine kinase inhibitor (*imatinib*)

Imatinib, which inhibits certain tyrosine kinase enzymes, is currently marketed as an oral therapy by Novartis (Basel, Switzerland) for chronic myelogenous leukemia (CML), gastrointestinal stromal tumors, and other malignancies (Gleevec in the United States,

Canada, and Israel; Glivec elsewhere, including Europe). Specifically, imatinib inhibits the tyrosine kinase activity of the Bcr-Abl oncoprotein, the stem cell factor c-kit, and the platelet-derived growth factor receptor (PDGF-R) kinases (de Kogel and Schellens, 2007).

PDGF seems to play an important role in the pathobiology of pulmonary vascular remodeling. In vitro, imatinib inhibits PDGF-induced proliferation and migration of cultured pulmonary artery smooth muscle cells from patients with idiopathic PAH, through blockage of PDGF-R phosphorylation (Perros et al., 2008). Moreover, drugs that inhibit both serine/threonine kinases and tyrosine kinases, including imatinib, have resulted in benefit in rat models of PH (Schermlay et al., 2005; Klein et al., 2008). Imatinib also showed benefit in chronically hypoxic mice with PH and a gain-of-function mutation of PDGF-R- β that resulted in development of significant pulmonary vascular remodeling (Dahal et al., 2011). In contrast to prolonged vasodilation associated with other PAH therapies, reversal of lung vascular remodeling through an antiproliferative effect is hypothesized to be the primary mechanism underlying the use of imatinib in PH; this effect is believed to be mediated by inhibition of lung PDGF (Schermlay et al., 2005), c-kit⁺ progenitor cells originating from bone marrow (Launay et al., 2012), or both. At clinical doses used, imatinib is thought to have no significant vasodilating effect on the pulmonary vasculature (Abe et al., 2011).

After an initial report of benefit from imatinib in a 61-year-old man with advanced PAH (Ghofrani et al., 2005), additional case reports suggested benefit in patients with concurrent PAH and chronic leukemia (Souza et al., 2006; Krauth et al., 2008) or PAH alone (Patterson et al., 2006; García Hernández et al., 2008; Overbeek et al., 2008; ten Freyhaus et al., 2009). As a result, a 6-month, placebo-controlled phase 2 trial was conducted in 59 patients with PAH (entry PVR greater than 300 dyne \cdot s/cm⁵) to evaluate the effects of imatinib (started at 200 mg and titrated to 400 mg once daily, if tolerated) (Ghofrani et al., 2010b). Patients were allowed to be receiving stable doses of background ERAs, prostanoids, or PDE-5 inhibitors (in varying combination) at study entry. Imatinib (compared with placebo) significantly improved PVR (mean treatment difference, -222 dyne \cdot s/cm⁵; $P < 0.01$) and cardiac output (mean treatment difference, 0.68 L/min; $P = 0.02$) but not 6-min walk distance (21.7 m). Post hoc analyses showed a more pronounced exercise capacity and hemodynamic treatment effect for subjects with more advanced disease (baseline PVR greater than 1000 dyne \cdot s/cm⁵).

A multinational, randomized, placebo-controlled phase 3 clinical trial (IMPRESS) enrolled 202 patients to evaluate 6 months of imatinib therapy (200 mg titrated to 400 mg once daily) as add-on treatment for patients with advanced PAH. Two unique features of this study, which reflect entry of patients with advanced PAH, are that

background therapy with prostanoids was allowed (in addition to an ERA or PDE-5 inhibitor, or both) and the entry PVR was required to be greater than 1000 dyne \cdot s/cm⁵ (later amended to greater than 800 dyne \cdot s/cm⁵). Preliminary results showed that imatinib significantly improved the mean 6-min walk distance over the 24-week period (32-m placebo-adjusted difference; $P = 0.002$) (Hoeper et al., 2011). In addition, imatinib also significantly improved key cardiopulmonary hemodynamics (PVR and mPAP; all $P < 0.001$). Discontinuations, which were more likely to be related to early intolerance due to drug- or PAH-specific adverse events than to disease progression, were more frequent with imatinib than placebo treatment (33 versus 18%). The most frequent adverse events with imatinib, which occurred in greater than 2% of patients in any treatment group but were more common with imatinib, were expected for the class of drug: nausea, peripheral edema, diarrhea, and vomiting. Three subjects in each treatment group died during the period from initiation of study drug until 30 days after last dose. Imatinib for the treatment of PAH is currently under regulatory review in the United States, EU, and Japan.

A second-generation tyrosine kinase inhibitor, nilotinib, has greater potency than imatinib to inhibit wild-type Bcr-Abl in a wide range of CML-derived and transfected cell lines (Breccia and Alimena, 2010). In addition, nilotinib also has inhibitory activity against the PDGF-R and c-Kit kinases, is more effective than imatinib in treating CML, and has fewer adverse events such as edema (Weisberg et al., 2006). In a monocrotaline rat model of PH, nilotinib reduced right ventricular pressure and percentage of muscularized lung vessels with efficacy similar to that of imatinib (Duggan et al., 2010). A 24-week, randomized, placebo-controlled, dose-ranging safety and efficacy study of nilotinib in patients with PAH is in progress (<http://clinicaltrials.gov> identifier NCT01179737).

B. Soluble guanylate cyclase stimulator (riociguat)

Riociguat is a first-in-class oral drug that directly stimulates soluble guanylate cyclase, both independently of endogenous NO and in synergy with NO (Mittendorf et al., 2009). In both hypoxic and monocrotaline rodent PH models, riociguat partially reduced PAH-associated structural and hemodynamic changes (Schermlay et al., 2008).

A single-dose hemodynamic study in 15 patients with PAH, CTEPH, or PH associated with mild to moderate interstitial lung disease reported that 1 or 2.5 mg of riociguat significantly improved cardiopulmonary hemodynamics, including mPAP and PVR, in a dose-dependent manner and to a greater extent than inhaled NO (Grimminger et al., 2009). Although riociguat had no selective pulmonary effect and decreased systemic blood pressure approximately 15 to 20% from baseline, no patient became hypotensive. Bayer subsequently con-

ducted an open-label, uncontrolled phase 2 trial of riociguat in 75 adult patients (42 with CTEPH and 33 with PAH, functional class II or III) (Ghofrani et al., 2010a). Riociguat given for 12 weeks (initial dose of 1.0 mg three times daily titrated every 2 weeks to a maximum of 2.5 mg three times daily) significantly improved median 6-min walk distance in patients with CTEPH (55 m) and with PAH (57 m). Riociguat also improved PVR ($-215 \text{ dyne} \cdot \text{s/cm}^5$), although 11 patients experienced asymptomatic hypotension. A large, 462-patient, placebo-controlled phase 3 trial evaluating 12 weeks of treatment with 1 or 2.5 mg of riociguat or placebo three times daily is ongoing (PATENT-1; <http://clinicaltrials.gov> identifier NCT00810693). The study is projected to be completed in 2012. Another study that is evaluating 270 patients with CTEPH randomized to 16 weeks of treatment with 1, 1.5, 2, or 2.5 mg of riociguat or placebo three times daily is also ongoing, with an estimated completion in 2012 (CHEST-1; <http://clinicaltrials.gov> identifier NCT00855465).

C. Nonprostanoid prostacyclin receptor agonist (selexipag)

Selexipag (ACT-293987) is a long-acting oral nonprostanoid prostacyclin receptor agonist (Kuwano et al., 2007). In April 2008, Actelion and Nippon Shinyaku Co. (Kyoto, Japan) signed a licensing agreement under which Actelion will be responsible for the global development and commercialization of selexipag outside Japan. The two companies will codevelop and cocommercialize the drug in Japan.

Selexipag may have greater pulmonary vasodilatory effects compared with other prostanoids because of its selectivity for the prostaglandin I_2 receptor (and not prostaglandin E receptor 3). In the monocrotaline rat model of PH, selexipag given twice daily for 19 days (for evaluation of right ventricular hypertrophy, pulmonary arterial wall hypertrophy, and relaxant response to acetylcholine in pulmonary artery preparations) or 45 days (for evaluation of survival) significantly improved all parameters (Kuwano et al., 2007).

A placebo-controlled phase 2a study evaluated 43 patients with PAH randomized three to one to receive selexipag or placebo over 17 weeks (Simonneau et al., 2012). All patients enrolled in the trial were receiving background therapy with an ERA or PDE-5 inhibitor or both. Treatment with selexipag was initiated at 200 μg twice daily and, if tolerated, increased in 200- μg increments to the maximum tolerated dose (800 μg twice daily) by day 35. Selexipag significantly improved PVR (primary endpoint) after 17 weeks of treatment (placebo-corrected reduction of 30.3%; $P = 0.0045$), although the increase in 6-min walk distance was not significant (placebo-adjusted change from baseline, 24.3 m; $P = 0.32$). The most commonly reported adverse events in selexipag-treated patients were headache, jaw pain, extremity pain, nausea, and nasopharyngitis.

Selexipag is currently being evaluated in a large, multinational phase 3 trial that is anticipated to enroll more than 670 patients into two arms (selexipag and placebo) and has a combined morbidity/mortality endpoint of time to first clinical worsening over a period of up to 3.5 years (GRIPHON trial; <http://clinicaltrials.gov> identifier NCT01106014). The estimated study completion date is 2013.

D. Tissue-targeting endothelin receptor antagonist (macitentan)

Actelion has developed a new orally active dual ERA (macitentan) for once-daily use. Macitentan has characteristics of lipophilic drugs, which can partition into local tissues (Iglarz et al., 2008). In contrast to other ERAs, which have limited tissue penetration, enhanced tissue-targeting properties may be of special relevance for effecting the vascular remodeling and possible inflammation of PAH (Iglarz et al., 2008). Inhibition of the bile salt export pump with intracellular accumulation of bile salts is believed to be a key mechanism of liver injury with bosentan (Fattinger et al., 2001); in contrast, macitentan does not increase circulating bile salts in rats and may also have a better liver injury profile (Sidharta et al., 2011).

In a monocrotaline rat model of PH, oral macitentan administered for 4 weeks prevented the development of PH and right ventricular hypertrophy (Iglarz et al., 2008). In a single-ascending-dose (0.2–600 mg) placebo-controlled phase 1 study in healthy men, the half-life of macitentan at a maximum tolerated dose of 300 mg was 17.5 h, and that of its pharmacologically active but less potent metabolite was 65.6 h (Sidharta et al., 2011). Macitentan also had no effect on total serum bile salt concentrations, although two subjects (one receiving 600 mg of macitentan and the other receiving placebo) had elevations in alanine aminotransferase levels. On the basis of plasma ET-1 concentrations, a 25-mg dose of macitentan was considered the lowest to fully block ET_A receptors.

In 2012, Actelion announced initial results of a pivotal 742-patient, multinational, double-blind, placebo-controlled study of macitentan (3 and 10 mg) treatment in patients with symptomatic PAH on background specific PAH therapy (SERAPHIN trial; <http://www.clinicaltrials.gov> identifier NCT00660179) (Actelion, 2012). Mean exposure was 85.3 weeks for the placebo group ($n = 249$), 99.5 weeks for patients receiving 3 mg ($n = 350$), and 103.9 weeks for patients receiving 10 mg ($n = 242$). Compared with placebo, macitentan decreased the risk of a morbidity/mortality event (primary endpoint) by 45% for the 10-mg group ($P < 0.00010$) and 30% for the 3-mg group ($P = 0.0108$). Macitentan (both doses) also significantly improved 6-min walk distance (change from baseline to 6 months), functional class (change from baseline to 6 months), and time to either death or hospitalization as a result of PAH over the treatment period. Elevations of

liver function enzymes greater than 3 times upper limit of normal occurred in 4.5% of patients receiving placebo, 3.6% of patients receiving 3 mg, and 3.4% of patients receiving 10 mg.

E. Serotonin transport inhibitor (escitalopram)

Serotonin (5-HT) is a potent pulmonary vasoconstrictor and pulmonary artery smooth muscle cell mitogen (MacLean et al., 2000; Launay et al., 2002). Hypoxia-induced remodeling of the pulmonary artery is increased in mice overexpressing the gene for the serotonin transporter (MacLean et al., 2004) or with restricted expression of 5-HT_{2B} receptors on bone-marrow cells (Launay et al., 2012). Appetite-suppressant drugs, such as dexfenfluramine, increase platelet serotonin release and increase risks of PH (Abenhaim et al., 1996); decreased platelet serotonin concentrations are more likely to occur in patients with PH than in control subjects (Ulrich et al., 2011).

Idiopathic PAH has been associated with both increased (Hervé et al., 1995) and normal (Lederer et al., 2008) free plasma serotonin levels, suggesting that plasma serotonin concentrations may not be the primary determinant of PH. Selective serotonin reuptake inhibitors, which increase plasma serotonin levels, and serotonin antagonists have prevented or reduced PH in multiple animal models (Guignabert et al., 2005; Porvasnik et al., 2010; Zopf et al., 2011). In patients, both retrospective and case-control studies suggest a relationship between use of selective reuptake inhibitors and decreased development of PAH (Kawut et al., 2006; Shah et al., 2009), although others have failed to find such a relationship (Dhalla et al., 2012).

Escitalopram (trade names Lexapro, Cipralex, Seroplex, Lexamil, Lexam) is an oral selective serotonin-reuptake inhibitor with high affinity for the human serotonin transporter. Escitalopram is approved in the United States (Forest Laboratories, New York, NY) and Europe (H. Lundbeck A/S, Copenhagen, Denmark) for several psychiatric indications in adults. A 30-patient randomized, placebo-controlled phase 2 trial evaluating the effects of escitalopram (30 mg/day) for 16 weeks in patients with mild to moderate PAH has completed (<http://clinicaltrials.gov> identifier NCT00190333). The primary outcome measure was exercise capacity (6-minute walk distance), with cardiopulmonary hemodynamics as a secondary measure. Results have not been publicly announced.

F. Serotonin receptor antagonist (terguride)

Terguride, which is approved in Japan as an oral agent for the treatment of hyperprolactinemia, is a partial dopamine agonist with potent serotonin (5-HT_{2B,2C}) receptor antagonist properties (Newman-Tancredi et al., 2002a,b). In May 2010, Pfizer acquired terguride from Ergonex Pharma GmbH (Appenzell, Switzerland) to de-

velop and commercialize the drug for the treatment of PAH (excluding Japan).

In vitro proliferation and migration of cultured primary human pulmonary artery smooth muscle cells were blocked by terguride (Dumitrascu et al., 2011). In addition, terguride inhibited in vitro 5-HT_{2A} receptor-mediated platelet aggregation (Kekewska et al., 2012) and reduced proliferation of pulmonary artery smooth muscle cells and pulmonary vasoconstriction in both prevention and treatment animal models of monocrotaline-induced PH (Dumitrascu et al., 2011). Details of a European phase 2 trial of terguride in PAH (TERPAH) have not been made public (Ergonex Pharma GmbH, 2008). Terguride received orphan drug designation in the EU (2007) and United States (2008) for the treatment of PAH and CTEPH.

G. Prostacyclin analog (beraprost-modified release)

Beraprost is a chemically stable and orally active prostacyclin analog that is absorbed rapidly in fasting conditions; peak concentration is reached after 30 min and elimination half-life is 35 to 40 min. Toray (Tokyo, Japan) initially manufactured beraprost under the brand name Dorner in Japan to treat peripheral vascular disease.

In 1995, beraprost was approved in Japan as a 3-to-4-times-daily administration for patients with idiopathic PAH under the brand names Procylin (Kaken Pharmaceuticals, Tokyo) and Dorner (Yamanouchi Pharmaceuticals, Tokyo). Approvals have also occurred in Thailand, Indonesia, the Philippines (under the trade name Dorner), and South Korea (Berasil). Initial approval was based in part on small, uncontrolled hemodynamic studies (Saji et al., 1996; Okano et al., 1997). A subsequent randomized, placebo-controlled trial evaluated beraprost treatment (median dose of 80 µg, given four times a day) for 12 weeks in 130 patients with PAH that was idiopathic/familial or related to either connective tissue disease, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV infection (Galié et al., 2002). Beraprost improved symptoms and exercise capacity (mean placebo-adjusted increase in 6-min walk distance of 25.1 m, $P = 0.036$), but not hemodynamics. However, a 1-year placebo-controlled study of 116 patients with PAH that was idiopathic or related to either connective tissue disease or congenital systemic-to-pulmonary shunts showed that the benefits of beraprost (maximum tolerated median dose, 120 µg four times a day) did not persist beyond 3 to 6 months (Barst et al., 2003b), limiting further regulatory approval of beraprost for PAH outside of Asia. After licensing of U.S. rights to United Therapeutics, a modified form with a longer duration of action [beraprost-modified release (MR)] was developed. In 2007, Toray received regulatory approval in Japan to use beraprost-MR in the treatment of PAH. In 2008, beraprost-MR was designated an orphan medicinal product by the EMA. In late 2011,

TABLE 3
Comparison of pivotal studies of approved therapies for chronic treatment of adult PAH in United States or EU

Agent	Trial Design and Study Population	Mean Change (Δ) in 6-min Walk Distance of Approved Doses						Treatment Effect	Approved Dose and Route	Most Common Adverse Effects	Current (2012) Label		Annual Cost	Reference
		Therapy	Baseline	Weeks of Trial		Δ	U.S.				EU ^a			
				12	16									
Epoprostenol (Flolan) (<i>n</i> = 81)	R, DB, compared with conventional treatment	Epoprostenol (<i>n</i> = 41)	316	348	32	47 (↑ 16%)	32	Continuous i.v.: 2 nkm, with increase 2 nkm every 15 min to tolerability	Flushing, headache, nausea, hypotension, jaw pain	PAH (WHO Group 1)		U.S. \$ 33–131K ^b	Barst et al. (1996)	
	IPAH (100%); class III (74%), IV (26%)	Conventional R _x (<i>n</i> = 40)	272	257	–15									
Treprostinil s.c. (Remodulin) (<i>n</i> = 470)	R, DB, PL	Treprostinil (<i>n</i> = 232) ^{c,d}	326	336	10	16 (↑ 5%) ^d	10	Continuous s.c.: 1.25 nkm, with weekly increase 1.25–2.5 nkm per tolerability	Infusion site pain, reaction, and bleeding; headache, diarrhea, nausea	PAH (WHO Group 1) or those transitioning from epoprostenol		59–149K ^b	Simonneau et al. (2002)	
	IPAH (58%); CTD (19%); CHD (23%); class II (11%), III (82%), IV (7%)	Placebo (<i>n</i> = 236)	327	327	0		0							
Treprostinil i.v. (Remodulin) (<i>n</i> = 16)	Prospective, open label	Treprostinil (<i>n</i> = 16)	319	400	82	82 (↑ 26%)	82	Continuous i.v.: 1.25 nkm, with ↑ similar to s.c.	Extremity/jaw pain, headache, diarrhea, headache, infection	PAH, class II to IV; unable to tolerate s.c.			Gomberg-Maitland et al. (2005)	
	IPAH (50%); CTD (38%); CHD (12%)											142K ^b	McLaughlin et al. (2010)	
Treprostinil inhaled (Tyvaso) (<i>n</i> = 235)	R, DB, PL	Treprostinil (<i>n</i> = 115) ^d	346	367	21	20 (↑ 5%) ^e	21	Inhaled: 18 μg (3 puffs) 4 times daily, with ↑ as tolerated 3 puffs every 1–2 weeks to target of 9 puffs (54 μg) 4 times daily	Cough, headache, throat irritation/pain, nausea, dizziness	PAH (WHO Group 1)				
	IPAH or HPAH (56%); CHD (31%); Other (13%); class III (98%), IV (2%)	Placebo (<i>n</i> = 120)	351	354	3		3							
Iloprost (Ventavis) (<i>n</i> = 203)	R, DB, PL	Iloprost (<i>n</i> = 120)	332	349	17	36 (↑ 11%)	17	Inhaled: 2.5 or 5 μg (1–2 puffs) 6–9 times daily	Flushing, headache, jaw pain, nausea, hypotension, trismus, syncope	PAH (WHO Group 1) IPAH, class III.		119–135K ^b	Oltschewski et al. (2002)	
	IPAH (50%); CTD (17%); CTEPH (28%); anorex (4%); class III (59%), IV (41%)	Placebo (<i>n</i> = 102)	315	297	–18		–18							
Bosentan (Tracleer) (<i>n</i> = 213)	R, DB, PL	Bosentan 125 mg b.i.d. (<i>n</i> = 74)	326	353	27	35 (↑ 9%)	27	Oral: 62.5 mg b.i.d. x 4 weeks, then 125 mg b.i.d. maintenance	Headache, flushing, rhinitis	PAH (WHO Group 1) PAH, class III		78K ^c	Rubin et al. (2002)	
	Idiopathic PAH (71%); CTD (29%); class III (92%); IV (8%)	Placebo (<i>n</i> = 69)	344	337	–8		–8		Other: anemia, hepatotoxicity, teratogenicity, ↓ male fertility					

TABLE 3—(Continued)
Comparison of pivotal studies of approved therapies for chronic treatment of adult PAH in United States or EU

Agent	Trial Design and Study Population	Mean Change (Δ) in 6-min Walk Distance of Approved Doses					Treatment Effect	Approved Dose and Route	Most Common Adverse Effects	Current (2012) Label		Annual Cost	Reference
		Therapy	Baseline	Weeks of Trial		Δ				U.S.	EU ^a		
				12	16								
Ambrisentan (Letairis/ Volibris) (n = 201)	ARIES-1: R, DB, PL IPAH (62%), CTD (30%), HIV (3%), anorex (2%); class I (2%), II (33%), III (58%), IV (7%)	Ambrisentan 5 mg (n = 67)	340	362	22	51 (↑ 15%)	Oral: 5 mg q.d. with increase to 10 mg q.d. as tolerated	No patients in any Ambrisentan group with had ↑ LFTs (> 3 ULN)	PAH (WHO Group 1)		78K ^c	Galié et al. (2005a)	
		Ambrisentan 10 mg (n = 67)	341	384	43								
		Placebo (n = 62)	342	334	-8								
Ambrisentan (Letairis/ Volibris) (n = 192)	ARIES-2: R, DB, PL IPAH (65%), CTD (32%), HIV (2%); class I (2%), II (45%), III (51%), IV (2%)	Ambrisentan 5 mg (n = 67)	355	404	49	59 (↑ 16%)		Most common side effects in both studies were peripheral edema, nasal congestion, sinusitis, and flushing (edema occurred in 28% of patients receiving 10 mg dose)	PAH, class III				
		Placebo (n = 65)	343	333	-10								
				388	42								
Sildenafil (Revatio) (n = 277)	R, DB, PL IPAH (63%), CTD (30%), CHD (7%); class I (0.4%), II (39%), III (58%), IV (3%)	Sildenafil 20 mg t.i.d.			45 (↑ 13%)		Oral: 20 mg t.i.d.	Headache, flushing, dyspepsia, back pain, diarrhea, limb pain, myalgia	PAH (WHO Group 1)	PAH (adults), class II,III PAH, ages 1–17 years	18K ^c	Galié et al. (2005b)	
		Placebo (n = 66)	348	344	-3								
Tadalafil (Adcirca) (n = 405)	R, DB, PL IPAH (62%), CTD (25%), CHD (8%); class I (1%), II (32%), III (65%), IV (2%)	Tadalafil 40 mg q.d. (n = 79)	352	392	40	33 (↑ 9%) ^f	Oral: 40 mg q.d.	Headache, diarrhea, nausea, back pain	PAH (WHO Group 1)	PAH, class II,III	14K ^c	Galié et al. (2009a)	
		Placebo (n = 82)	343	351	7								

↑, increase; ↓, decrease; b.i.d., twice daily; CHD, congenital heart disease; CTD, connective tissue disease; DB, double-blind; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary hypertension; i.v., intravenous; K, thousand; n.km, ng · kg^{–1} · min^{–1}; PL, placebo; q.d., once daily; R, randomized; s.c., subcutaneous; t.i.d., three times daily; ULN, upper limit of normal.

^a European labels reflect drugs with central approval by EMA and not approval in various countries on a national basis through the mutual recognition process.

^b Average annual cost per claim (Massachusetts Executive Office of Health and Human Services, 2011).

^c Data from two separate trials pooled for analysis and reported in regulatory submissions. Subgroup analysis (Simonneau et al., 2002) and additional studies (Mathier et al., 2010) have shown increased efficacy with ability to up-titrate dose.

^d Six-min walk values shown are within-treatment median change from baseline and median difference between groups at week 12 (treatment effect).

^e Red Book (2010).

^f Six-min walk distance change in subjects not receiving concomitant bosentan was 44 m for 40-mg group.

United Therapeutics announced that a 36-patient, 12-week phase 2 trial evaluating three doses of bera-prost-MR added to background therapy (<http://clinicaltrials.gov> identifier NCT00989963) failed to meet its primary hemodynamic endpoint and that trials with new dosing regimens were being designed.

H. Endothelial nitric oxide synthase (cicletanine)

Cicletanine is a once-daily oral drug initially developed by Ipsen (Paris, France) and approved in Europe for use as monotherapy in the treatment of systemic hypertension. In 2005, Ipsen licensed the rights to Navitas (Laramie, WY) to develop cicletanine as combination therapy worldwide and as monotherapy in the United States. In May 2008, Gilead Sciences acquired all Navitas assets related to cicletanine. In 2009, cicletanine was granted orphan drug status for treatment of PAH by the FDA.

Preclinical data suggest that cicletanine may enhance vascular NO availability by augmenting the activity of endothelial NO synthase or potentiating the vasodilator effect of atrial natriuretic peptide (Jin et al., 1992; Kalinowski et al., 2001). In 2009, Gilead initiated a randomized, placebo-controlled, dose-ranging phase 2 study of cicletanine in 160 patients with PAH (<http://clinicaltrials.gov> identifier NCT00832507). Subjects were randomized to cicletanine doses of 150 mg once daily, 150 mg twice daily, 300 mg once daily, or placebo for 12 weeks, with 6-min walk distance as the primary efficacy endpoint and cardiopulmonary hemodynamics as a secondary outcome. Monotherapy or combination therapy with an ERA, PDE-5 inhibitor, or parenteral prostanoid was allowed at entry. The study was completed in 2012 and results have not been publicly announced.

I. Gene therapy with progenitor endothelial cells

Endothelial progenitor cells (EPCs) may be involved in the pathobiology of PAH (Fadini et al., 2010; Launay et al., 2012). Transplantation of EPCs resulted in significant improvement in multiple animal models of PH (Nagaya et al., 2003; Takahashi et al., 2004; Yip et al., 2008). Furthermore, an increase in circulating EPCs may contribute to the benefits of prostanoids and PDE-5 inhibitors in PAH (Diller et al., 2008; Smadja et al., 2011). A randomized, uncontrolled pilot study of 31 patients with idiopathic PAH (15 receiving autologous EPCs, 16 receiving conventional therapy) showed that infusion of autologous EPCs seemed to be safe and, compared with patients receiving conventional therapy, study participants showed significantly improved exercise capacity and hemodynamics after 12 weeks (Wang et al., 2007).

Lung LLC (Silver Spring, MD) is a wholly owned subsidiary of United Therapeutics, and Northern Therapeutics, Inc. (Montreal, Canada) is its Canadian affiliate. In 2006, Northern Therapeutics, Inc., initiated an open-label trial in Canada termed PHACet (Pulmonary

Hypertension Assessment of Cell Therapy) in patients with PAH involving use of autologous EPCs engineered using a vector containing the gene for human endothelial NO synthase. Eighteen patients with idiopathic, heritable, or anorexigen-associated PAH are planned for enrollment in this dose-escalation study, which will evaluate long-term safety (5-year) and short-term efficacy (exercise capacity and hemodynamics at 3 months) as the main outcome measures. The anticipated completion date is 2013 (<http://clinicaltrials.gov> identifier NCT00469027).

IV. Comparison of Approved Therapies

Comparing PAH therapies across studies is limited by trial enrollment differences for key baseline factors that predict efficacy, including PAH etiology, 6-min walk distance, functional class, hemodynamics, and the PAH-specific therapies available at the time of the trial. Differences in whether a study was conducted in treatment-naïve patients (no longer considered ethical given the availability of PAH therapies) or as add-on treatment (to mono-, dual-, and triple background therapy) also limit comparisons.

Examples of how baseline covariates affect treatment effects and limit comparison of drugs that are not evaluated within the same trial are as detailed below.

- In STRIDE-1, 100 mg of sitaxentan ($n = 55$) and 300 mg ($n = 63$) given for 12 weeks resulted in a placebo-adjusted treatment effect for 6-min walk distance of 33 to 35 m (Barst et al., 2004a). STRIDE-1 was the first trial of an ERA therapy that allowed entry of patients with functional class II (mild) status. Of 178 treated patients, 59 (33%) had functional class II status, 117 (66%) had functional class III (moderate) status, and 2 (1%) had functional class IV (severe) status at baseline. As a result of inclusion of patients with mild symptoms, the 6-min walk distance at baseline for patients in STRIDE-1 (mean \pm S.D., 398 ± 110 m; range, 79–657 m) was 20 to 30% higher than in previous trials with other PAH agents. In a post hoc analysis, a subset of patients who met more traditional but narrower entry criteria (functional class III/IV PAH that was idiopathic or associated with connective tissue and a maximum baseline 6-min walk distance of 450 m) were evaluated. The resultant (placebo-adjusted) treatment effect for pooled sitaxentan doses increased to 65 m (Barst et al., 2004a). A subsequent study of sitaxentan that enrolled most patients (61%) with PAH functional class II status at baseline failed to show a 6-min walk distance treatment effect over 18 weeks (Sandoval et al., 2012).
- Treprostinil (as a continuous subcutaneous infusion) was the first PAH therapy to include mildly impaired (functional class II) patients in a clinical

trial (Simonneau et al., 2002). In the pivotal phase 3 trial, the treatment effect of treprostinil in 53 patients with functional class II status was 2 m compared with 17 m for the 382 patients who had functional class III status and 54 m for the 34 patients who had functional class IV status.

- In the pivotal trial of tadalafil, the placebo-adjusted change in 6-min walk distance in patients with functional class I and II status was 24 m compared with 36 m in patients with functional class III and IV status (Galié et al., 2009a).

There have been a considerable number of PAH combination (add-on) trials, but only two comparator trials have been conducted with PAH therapies:

- A double-blind, randomized trial compared sildenafil with bosentan in 26 patients with idiopathic PAH and functional class III symptoms (SERAPH trial) (Wilkins et al., 2005). Treatment was 1) 50 mg of sildenafil twice daily for 4 weeks and then three times daily for 12 weeks or 2) 62.5 mg of bosentan twice daily for 4 weeks then 125 mg twice daily for 12 weeks. Subjects receiving sildenafil had a 114-m gain in 6-min walk distance ($P = 0.0002$) compared with 59 m for subjects receiving bosentan ($P = 0.001$).
- STRIDE-2 randomized 245 subjects with symptomatic PAH that was idiopathic, associated with connective tissue disease, or associated with congenital heart disease (Barst et al., 2006b). Subjects received open-label bosentan (125 mg twice daily), sitaxentan (50 or 100 mg once daily), or placebo (once daily) for 18 weeks. Sitaxentan (100 mg; 31 m, $P = 0.03$) and bosentan (29.5 m, $P = 0.05$) significantly improved 6-min walk distance compared with placebo treatment.

These findings underscore differences in trial designs and study populations that may provide treatment results. The comparator 16-week SERAPH trial showed significant improvements in 6-min walk distance (114 m with sildenafil, 59 m with bosentan) that were probably the result of enrollment of patients with features that predict the best treatment response: 1) entry of subjects only with idiopathic PAH, 2) exclusion of subjects with mild disease (functional class II), and 3) a longer trial duration (16 weeks) than most studies conducted previously (12 weeks). Table 3 compares treatment effects from clinical trials of approved long-term PAH therapies. The table also summarizes route of administration, doses, adverse events, regulatory approvals, and costs.

V. Conclusion

PAH remains a treatable yet progressive disease, often leading to right-sided heart failure and death. The average life expectancy of patients with PAH in the current treatment era is estimated at 5 to 7 years after

diagnosis, with significant morbidity. The last few decades have yielded important advances in the understanding of PAH that have led to pharmacological therapies that have reduced both morbidity and mortality despite challenges of parenteral or inhaled delivery systems, toxicities requiring laboratory monitoring, frequent dosing schedules, variable efficacy, and cost. Upcoming patent expirations of PAH drugs have the potential to alter the cost of treatment of the disease. The pipeline for PAH drug development is promising, with novel therapies in new classes being investigated. The potential to target new pathways, the seriousness of the disease, and the eventual deterioration of patients on monotherapy also makes development of novel drugs for use as combination therapy a necessity.

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