Over the last 2 decades, the treatment of patients with pulmonary arterial hypertension (PAH) has undergone a dramatic transition. The US Food and Drug Administration (FDA) approval of epoprostenol as the first PAH-specific therapy in 1996 made a substantial impact on the way PAH was treated, and led the way for the development of additional PAH-specific therapies. Subsequently, between 2001 and 2009, 8 new therapies were approved. In general, these drugs target 1 of 3 major pathophysiologic pathways in PAH: the prostacyclin pathway, the nitric oxide (NO) pathway, and the endothelin-1 (ET-1) pathway, with prostacyclin and NO being vasodilators and inhibitors of pulmonary artery smooth muscle cell (PASMC) proliferation, and ET-1 being a vasoconstrictor and stimulator of PASMC growth. While the pathophysiology of PAH is multifactorial and complex, a deficiency in prostacyclins and NO as well as an excess of ET-1 have been identified as major disease mediators. However, despite the development of several new pharmacological treatments targeting these pathways, no cure for PAH exists, and 3-year mortality remains unacceptably high at 55%. In addition, the use of several PAH drugs is limited by complex regimens as well as administration-related complications and drug-related side effects. The year 2013 represents a milestone in PAH treatment, with the approval of 3 new oral PAH drugs. These drugs include macitentan, riociguat, and treprostinil; all 3 target different pathophysiologic pathways and will be reviewed in this article.

MACITENTAN
Pharmacology and Mechanisms of Action
Macitentan (Opsumit®) is a novel dual endothelin receptor antagonist (ERA). Like the older ERA antagonist bosentan, macitentan blocks the effects of ET-1 at its 2 main receptors (ET\textsubscript{A} and ET\textsubscript{B}; Figure 1, left column). The dual action contrasts with the mechanism of action of ET\textsubscript{A}-selective ERAs like ambrisentan, which only antagonize ET-1 effects at the ET\textsubscript{A} receptor. In contrast to older ERAs, macitentan exhibits increased tissue penetrance and thus is purported to have increased efficacy and safety. The half-life of macitentan after oral administration is 15 hours. A peak serum concentration is reached approximately 8 hours after ingestion. There is a dose-dependent effect, with a more pronounced effect noted with administration of 10 mg over 3 mg, as demonstrated by a 2-fold increase in plasma ET-1 levels. Side effects are similar to those of other ERAs; however, macitentan seems to...
Patients enrolled had to be in WHO functional class II, III, or IV with a 6-minute walk distance (6MWD) of <500 m. WHO functional class at Month 6, and hospitalization for PAH, and death or hospitalization for PAH, and worsening of PAH. This trial was unique as it was the first long-term, event-driven trial to be published in the PAH field. In contrast to prior studies, the authors did not use the “classical” PAH trial design with evaluation of 6MWD after 12 to 14 weeks of therapy as the primary endpoint; rather, they established “hard” clinical endpoints such as death, hospitalizations, escalation of therapy, and worsening of PAH. This is particularly relevant, as the significance of 6MWD and even hemodynamic parameters as surrogate endpoints for clinical events in PAH trials has recently been questioned.3-10 The event-driven trial design with evaluation of the drug over a median treatment period of 115 weeks is clearly a major step forward and sets a new standard in PAH research, a notion emphasized at the 2013 World Symposium on Pulmonary Hypertension (PH).11 It should be mentioned, however, that while treatment with macitentan significantly decreased the composite endpoint of worsening PAH in 84 patients (33.6%) in the placebo group, 65 patients (26.0%) in the macitentan 3 mg group, and 50 patients (20.7%) in the 10 mg group. Of note, hospitalization rather than death accounted for most of these events. At Month 6, the 6MWD decreased by a mean of 9.4 meters in the placebo group. In the macitentan arm, the 6MWD increased by a mean of 7.4 meters and 12.5 meters in the 3 and 10 mg groups, respectively. WHO functional class improved in 13% of the patients in the placebo group, as compared with 20% in the 3 mg group and 22% in the 10 mg group.

As expected, compared with patients who received placebo, more patients in the macitentan arms exhibited nasopharyngitis, headache, and anemia. The effect on hemoglobin was dose-dependent, with the rate of anemia reaching 13.2% in the macitentan 10 mg group; 4.3% of patients in this group had a hemoglobin ≤8 mg/dL. Importantly, no significant differences in hepatotoxicity were noted among the 3 groups. No statistical differences in discontinuation of therapy occurred with placebo vs study drug in the doses tested.

Strengths and Limitations of SERAPHIN

This trial was unique as it was the first long-term, event-driven trial to be published in the PAH field. In contrast to prior studies, the authors did not use the “classical” PAH trial design with evaluation of 6MWD after 12 to 14 weeks of therapy as the primary endpoint; rather, they established “hard” clinical endpoints such as death, hospitalizations, escalation of therapy, and worsening of PAH. This is particularly relevant, as the significance of 6MWD and even hemodynamic parameters as surrogate endpoints for clinical events in PAH trials has recently been questioned.3-10 The event-driven trial design with evaluation of the drug over a median treatment period of 115 weeks is clearly a major step forward and sets a new standard in PAH research, a notion emphasized at the 2013 World Symposium on Pulmonary Hypertension (PH).11 It should be mentioned, however, that while treatment with macitentan significantly decreased the composite endpoint of worsening PAH
or death, the major driver of this reduction was fewer instances of worsening PAH rather than fewer deaths.

One weakness of the trial was that the increase in 6MWD (treatment effect with 10 mg dose vs placebo /H11005 22 meters) did not reach the recently defined threshold for clinical significance.8,9 Another criticism of the trial was the heavy influence of industry. The trial was funded by the drug manufacturer, an outside writer was paid to draft the manuscript, and statistics were gathered by the pharmaceutical company. The publishing journal did perform an external independent statistical evaluation of the data and confirmed its results. Lastly, similar to previous trials, SERAPHIN fails to clearly demonstrate that ERA use reduces all-cause or PAH-specific mortality.

Clinical Implications
The results of SERAPHIN led to the approval of macitentan for PAH patients. The FDA-approved dose is 10 mg once daily. The FDA requires no liver function testing after baseline testing, but is requiring the drug manufacturer to keep a registry (OPsmumit USers Registry [OPUS]; Clinical Trials.gov identifier: NCT02126943) to monitor hepatotoxicity in the postmarketing setting. Hemoglobin levels should be monitored. Like other ERAs, macitentan is teratogenic and can only be prescribed through a Risk Evaluation and Mitigation Strategy (REMS) program. The Updated Treatment Algorithm of PAH from the Fifth World Symposium on PH gives a class I recommendation for macitentan for PAH patients in WHO functional class II or III, and a class IIa recommendation for macitentan for PAH patients in WHO functional class IV.2

ROICIGUAT
Pharmacology and Mechanism of Action
Riociguat (Adempas8) is the first FDA-approved soluble guanylate cyclase (sGC) stimulator for PAH. As shown in Figure 1, sGC works in the NO pathway by converting guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), a second messenger that mediates vasodilation and inhibits PASMC proliferation. There is also evidence that cGMP exerts anti-inflammatory and anti-thrombotic effects in the lung, as well as inotropic effects in the right ventricle (RV).12,13 PAH, however, is a NO-deficient state, thus resulting in decreased sGC activation and cGMP generation.3,14 Riociguat restores sGC activity through 2 distinct mechanisms: first, it increases the sensitivity of reduced sGC to endogenous NO by stabilizing NO binding to sGC’s prosthetic heme group.12 Secondly, riociguat increases activity of reduced sGC independently of NO.12 Riociguat is rapidly absorbed, and maximum plasma concentrations are reached between 0.5 and 1.5 hours. The mean elimination half-life appears to be 5 to 10 hours.15 The NO-independent action of riociguat distinguishes it from PDE5Is, which require NO to be bioavailable and theoretically may have limited effect in the presence of low endogenous NO levels.

Clinical Evaluation in the PATENT-1 Trial
The Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) is a Phase 3, randomized, multicenter, placebo-controlled trial that evaluated riociguat’s efficacy in PAH.16 Patients with symptomatic PAH (idiopathic, familial, or associated with connective-tissue disease, congenital heart disease, portal hypertension, or anorexigen or amphetamine use) were included if they had a pulmonary vascular resistance (PVR) >300 dynseccm⁻⁵, a mean pulmonary artery pressure (mPAP) ≥25 mm Hg, and 6MWD of 150 to 450 meters. Treatment-naïve patients and patients receiving treatment with ERAs or prostanoids (excluding intravenous prostanoids) at doses stable ≥90 days were eligible; patients receiving PDE5Is were not eligible. Patients were enrolled in a 2:4:1 ratio: placebo, riociguat capped at 2.5 mg 3 times daily (tid), and riociguat capped at 1.5 mg tid. Riociguat
dosing started at 1 mg tid and was titrated using systemic blood pressure, ranging from 0.5 to 2.5 mg tid. The dose was titrated until Week 8 and then continued at that dose for another 4 weeks. All patients completing the initial 12-week study were eligible to enter an extension trial (PATENT-2; ClinicalTrials.gov identifier: NCT00863681). The primary endpoint was the change in 6MWD from baseline to the end of Week 12. Secondary efficacy endpoints included changes in PVR, N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels, WHO functional class, time to clinical worsening, Borg dyspnea score, and quality of life measures. Clinical worsening was defined as death, heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of PAH, start of new PAH-specific treatment or escalation of a preexisting prostanooid treatment due to worsening PAH, or persistent decrease in 6MWD due to worsening PAH.

The study included 443 patients (126 on placebo, 317 on study drug); 95% of patients were either in WHO functional class II or III at the time of enrollment. Forty-four percent and 6% of patients were on background ERA and inhaled prostanooid therapy, respectively. Since the 1.5 mg regimen was strictly exploratory, these data will not be discussed further, and the rest of the review will focus on the 2.5 mg regimen. At Week 12, the primary endpoint of 6MWD increased by a mean of 30 meters in the riociguat arm, while it decreased by 6 meters in the placebo group (Figure 3). Several secondary endpoints (PVR, NT-proBNP levels, WHO functional class, and Borg dyspnea score) were also positively affected by riociguat. For example, PVR decreased by 223 dynsec–cm–5. Additionally, there was a lower incidence of events indicating clinical worsening in the riociguat arm. The side effect profile of riociguat was similar to that of other drugs enhancing cGMP signaling, with headache, dyspepsia, peripheral edema, nausea, dizziness, and diarrhea being the most common. Syncope occurred in 1% of riociguat patients and 4% of placebo patients. No significant differences occurred with regard to worsening PH, chest pain, and RV failure. It is worth noting that hypotension occurred more frequently in the riociguat group (10% vs 2%). Of the 25 cases of hypotension in the riociguat arm, the authors characterized 16 as mild, 8 as moderate, and 1 as severe. The benefits associated with riociguat treatment were sustained at 24 weeks.

Clinical Evaluation in the CHEST-1 Trial
The publication of PATENT-1 was accompanied by publication of the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1), a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the effectiveness of riociguat in inoperable or persistent (after pulmonary thromboendarterectomy [PTE]) chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH, a consequence of incompletely resolved pulmonary emboli, is categorized as Group 4 PH, but shares pathophysiological and structural features with Group 1 PAH. While CTEPH is surgically curable via PTE, there has been long-standing interest in medical therapy for inoperable or persistent cases of the disease. CHEST-1 is the largest prospective, randomized trial evaluating the role of PAH-specific therapy for CTEPH. CTEPH patients 18 to 80 years of age were included if their disease was adjudicated to be technically inoperable or if they had persistent or recurrent PH following PTE. Additional inclusion criteria included mPAP, PVR, and 6MWD—identical to PATENT-1. Patients were excluded if they had received an ERA, prostacyclin analogue, PDE5I, or NO donor ≤3 months before study entry; 262 patients were included and randomized in a 1:2 fashion into the placebo or riociguat arm. The riociguat target dose was 2.5 mg tid, which was achieved in 77% of riociguat patients. Patients that com-
completed the 16-week study period were eligible to participate in a long-term, open-label extension study (CHEST-2; ClinicalTrials.gov identifier: NCT00910429).

As in PATENT-1, the primary endpoint was the change in 6MWD. Similarly, secondary efficacy endpoints were identical to PATENT-1 (see above); 95% of enrolled patients were in WHO functional class II or III at the time of enrollment. Seventy-two percent of all patients were deemed inoperable, while 28% had postoperative persistent or recurrent PH. At Week 16, the 6MWD increased from baseline by a mean of 39 meters in the riociguat group, as compared with a mean decrease of 6 meters in the placebo group (Figure 4). While this improvement in 6MWD was observed in patients ineligible for surgery and in those with persistent/recurrent PH after surgery, effects appeared to be more pronounced in the first group (54 meters vs 26 meters, respectively).

Riociguat treatment was also associated with significant improvement in PVR and other hemodynamic variables, including mPAP and cardiac output. Levels of NT-proBNP were significantly reduced, and WHO functional class and dyspnea improved. There was, however, no significant difference in the incidence of clinical worsening events between riociguat and placebo. Riociguat’s side effect profile was similar to what was observed in PATENT-1. Hypotension occurred in 9% of patients (vs 3% of placebo patients), evenly divided between mild and moderate (8 patients each). Hemoptyis occurred in 2% of riociguat patients; this was not noted in placebo patients. There were no differences in the rates of syncope or RV failure between groups. An exploratory analysis of the first 12 weeks of the open-label CHEST-2 extension trial demonstrated further increases in 6MWD.

Strengths and Limitations of PATENT-1 and CHEST-1

The 2 riociguat trials are remarkable for several reasons. First, they are evaluating a drug with a new mechanism of action, thus expanding the armamentarium of PAH-specific therapies. Most importantly, CHEST-1 is the largest prospective evaluation of a medical treatment for inoperable or recurrent/ persistent CTEPH. Its results were more robust than those of a previous trial evaluating bosentan for inoperable CTEPH; the latter trial, while demonstrating improvements in hemodynamics, did not show any improvement in exercise capacity. CHEST-1 led to the approval of riociguat for inoperable and persistent/recurrent CTEPH, making it the first FDA-approved medical therapy for this disease.

A potential weakness of the riociguat trials is the “traditional” short-term design with evaluation of the 6MWD as the primary endpoint. The increase in 6MWD, however, was in the clinically meaningful range for both studies. The long-term benefits and side effects of the drug are not yet known; therefore, the results of the extension studies will be of utmost interest. Preliminary results (presented in abstract form) suggest that the long-term use of riociguat is safe and effective. The accompanying editorial for PATENT-1 and CHEST-1 identified several additional issues. cGMP likely has positive inotropic effects on RV function, so the lack of a thorough investigation of effects of riociguat on the RV represents a “missed opportunity.” Also, while the study authors were responsible for the draft manuscript, editorial assistance was provided by a company supported by the sponsor, and the statistician was employed by the study sponsor.

While the approval of a medical therapy for CTEPH is a major step forward in the field, there is concern that physicians may be tempted to start the drug on operable patients if there is no local surgical expertise for this disease. It cannot be overemphasized that the treatment of choice for CTEPH is PTE, as it is a more potent intervention with the potential to cure the condition. Medical therapy should only be offered...
if surgery is not possible or if the disease recurs/persists after surgical intervention.\(^\text{18}\)

**Clinical Implications**

The results of PATENT-1 led to the approval of riociguat for patients with Group 1 PAH. As mentioned above, the drug is also the first to be approved for inoperable and persistent or recurrent Group 4 CTEPH after PTE. The FDA-approved dose is 2.5 mg tid. The drug is usually uptitrated in 0.5 mg increments; close attention must be paid to systemic blood pressure during the uptitration process. Some patients may not tolerate the target dose and can be treated with a lower dose. Concomitant use of PDE5Is, nonspecific PDE5Is (dipyridamole and theophylline), or other NO donors is contraindicated. Riociguat is teratogenic and can only be prescribed through a REMS program. The treatment algorithm from the Fifth World Symposium on PH gives a class I recommendation for riociguat for PAH patients in functional class II or III, and a class IIa recommendation for riociguat for PAH patients in functional class IV.\(^\text{2}\)

Riociguat is also being evaluated for Group 2 and Group 3 PH, with the published results of a pilot and a Phase 2 trial being mixed.\(^{22,\text{23}}\)

**TREPROSTINIL**

**Pharmacology and Mechanism of Action**

Treprostinil diolamine (Orenitram\(^\text{®}\)) is a novel oral prostacyclin analogue (Figure 1, right column). The sodium salt of treprostinil as well as other prostacyclin analogues have been available in intravenous, subcutaneous, and inhaled forms for years.\(^\text{2}\) However, because of the complexity and side effect profile of several of the parenteral therapies, there has been long-standing interest in oral prostacyclin therapy. Treprostinil diolamine has several advantages over parenteral prostacyclins. Beyond the typical advantages associated with oral therapy, there is a convenient twice-daily (bid) dosing regimen and no requirement for cooling the drug. The half-life of the drug is approximately 4.5 hours, with a broad and sustained blood concentration for approximately 8 hours after a single oral dose.\(^\text{24}\)

**Clinical Evaluation in the FREEDOM-M Trial**

The Oral Treprostinil as Monotherapy for the Treatment of PAH (FREEDOM-M) trial was the pivotal trial that evaluated monotherapy with oral treprostinil.\(^\text{25}\) The trial was designed to assess the safety and efficacy of oral treprostinil therapy in de novo PAH patients not concurrently receiving other forms of FDA-approved PAH-specific therapies. FREEDOM-M was developed after earlier trials (FREEDOM-C and FREEDOM-C2) did not achieve their primary endpoint and/or were plagued by adverse effects from the study drug.\(^{26,\text{27}}\) The original starting dose was 1 mg bid. However, as many side effects in the earlier oral treprostinil trials were attributed to high starting doses and large dose increments, lower-dose formulations were developed and the trial was amended to allow starting doses as low as 0.5 mg bid, and eventually 0.25 mg bid. Eligible patients were 12 to 75 years of age with idiopathic or hereditary PAH (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥5 years), or PAH associated with collagen vascular disease or HIV. Patients were ineligible if they had received ERA, PDE5Is, or prostacyclin therapy ≤30 days of baseline. Baseline 6MWD was required to be 100 to 450 meters. The primary endpoint was the effect of oral treprostinil on exercise capacity compared with placebo, as measured by the change in 6MWD from baseline to Week 12. Secondary endpoints included Borg dyspnea score, combined 6MWD/Borg dyspnea score, dyspnea-fatigue index, WHO functional class, symptoms of PAH, clinical worsening, and safety. Clinical worsening was defined as one of the following: cardiovascular death, transplantation, atrial septostomy, or clinical deterioration, with the latter being defined as the initiation of new, approved PAH-specific therapy (ERA, PDE-5Is, or prostacyclin) plus either hospitalization for decompensated PAH or a ≥20% decrease in 6MWD from baseline combined with worsening WHO functional class; 349 patients were randomized in a 2:1 fashion to drug or placebo. Thirty-four percent of participants were WHO functional class II and 66% were functional class III. All patients receiving the study drug were labeled as intention to treat (ITT); a subgroup of patients with access to the 0.25 mg tablet was labeled as modified intention to treat (mITT). The study drug was titrated based on each participant’s clinical response and tolerability. The mean dose of study drug achieved in the mITT population at Weeks 4, 8, and 12 was 2.3±1.3, 3.2±1.9, and 3.4±1.9 mg bid, respectively.

At 12 weeks of therapy, the average increase in 6MWD was 23 meters in the mITT arm and 26 meters in the ITT arm when compared to placebo (Figure 5). For the mITT patients, there was a significant improvement in the combined 6MWD/Borg dyspnea score at Week 12. For the ITT population, significant improvements occurred in the combined 6MWD/Borg score at Weeks 4, 8, and 12. No differences in clinical worsening were observed between treatment groups for either population. Of note, there was an exceptionally high amount of adverse events in both the treprostinil and placebo arms (88% to 94% of all patients had ≥1 adverse event). Typical prostacyclin side effects such as headache, nausea, diarreha, jaw pain, and vomiting were the most common adverse events in the treprostinil group and occurred in 24% to 69% of patients. These events were considered severe in intensity in 10% to 40% of patients, with headache being the most common severe adverse event. Ten percent of patients in the ITT arm withdrew from the study due to adverse effects.

**Strengths and Limitations of FREEDOM-M**

The major milestone reached with FREEDOM-M is that the trial led to the FDA approval of the first oral prostacyclin in the United States. The slow and gradual uptitration with small increments overcame problems with drug delivery and tolerability that arose in earlier trials of oral treprostinil.\(^{26,\text{27}}\) Nevertheless, even in FREEDOM-M, the rate of significant side effects was still substantial. The trial is limited by its
short duration (12 weeks), and the large Asian population included raises questions about extrapolation of the data to Western populations. While the average improvement in 6MWD of 26 meters is modest, the observation that about a third of patients improved 6MWD by >50 meters suggests that some may respond to the drug better than others (eg, those who tolerated higher doses).28 Despite this fact, several of the secondary endpoints (eg, clinical worsening) were not met.

Table 1. Overview of oral PAH therapies approved in 2013. 6MWT = 6-minute walk test; BNP = B-type natriuretic peptide; Diagn. = Diagnostic; WHO = World Health Organization

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Primary Trial and Reference</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>WHO Diagn. Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan</td>
<td>Dual endothelin receptor antagonist</td>
<td>SERAPHIN7</td>
<td>Event driven study of a composite end point of death, atrial septostomy, lung transplantation, initiation of continuous prostanooids, or worsening of PAH</td>
<td>Change in 6MWT distance and WHO functional class compared to placebo</td>
<td>1</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Soluble guanylate cyclase stimulator</td>
<td>PATENT-1 and CHEST-116,17</td>
<td>6MWT distance</td>
<td>Changes in hemodynamics, BNP, and WHO functional class compared to placebo</td>
<td>1 and 4</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Prostacyclin analogue</td>
<td>FREEDOM-M25</td>
<td>6MWT distance</td>
<td>Changes in Borg score, PAH symptoms, and clinical worsening</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical Implications
The results of FREEDOM-M led to the approval of oral treprostinil for PAH patients in order to enhance exercise capacity. The recommended starting dose is 0.25 mg bid; the recommended titration schedule is by 0.25 mg or 0.5 mg bid or by 0.125 mg tid every 3 to 4 days as tolerated. The maximum dose is determined by tolerability. The side effect profile, complex dosing regimen, modest improvement in 6MWD, and lack of long-term data raise questions about the place of oral treprostinil in the PAH treatment algorithm. Due to the FDA approval of oral treprostinil late in 2013, the drug was not included in the updated treatment algorithm from the Fifth World Symposium on PH. Some experts advocate for oral treprostinil in those patients who meet criteria for parenteral prostacyclin, but have barriers or reluctance to switch to these drugs with their complex administration regimens. However, it should be noted that no data exist that suggest a similar potency of oral treprostinil when compared to the parenteral regimens. In addition, patients requiring therapy escalation to parenteral prostacyclin typically are on concomitant therapy with oral PAH drugs, and FREEDOM-C and FREEDOM-C2 did not show benefit of oral treprostinil when given in combination with other PAH medications.26,27 Another potential approach would be to start oral treprostinil early in the course of the disease, making prostacyclin

Figure 5: Effect of oral treprostinil on 6MWD in FREEDOM-M. Change in 6MWD from baseline at Weeks 4, 8, and 12 (means ± SD; recorded at estimated peak plasma study drug concentrations) is shown. Data for Week 11 (means ± SD) were recorded at estimated trough plasma study drug concentrations. Modified intent-to-treat (mITT) population is shown in light gray; intent-to-treat (ITT) population is depicted in dark gray. Doses listed are mean oral treprostinil doses (twice daily) ± SD for completers at each study time point. Reproduced with permission from Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. Circulation. 2013;127(5):624-633.
therapy available to a larger group of patients, but such an approach requires further study.

CONCLUSION
The year 2013 delivered an explosion in new oral treatment regimens for WHO Group 1 and Group 4 PH (summarized in Table 1). In a disease with significant morbidity and mortality, this is a major step forward. While some of the new oral drugs represent major milestones (riociguat for inoperable or residual/recurrent CTEPH; macitentan for PAH), the role of others (riociguat and oral treprostinil for PAH) in the treatment algorithm is more difficult to define. The SERAPHIN trial has established a new standard for clinical trial design, and the field will benefit from the introduction of more long-term and event-driven trials. While these are exciting times for PAH patients, their care providers, and the medical profession, several questions remain. What is the long-term safety and efficacy profile of the new oral drugs? Are the SERAPHIN results so strong that patients should be switched from older ERAs to macitentan? What will be the role (and cost) of older PAH drugs once they become generic (eg, bosentan)? Is there a role for up-front combination therapy in PAH? Where will drugs with new treatment mechanisms (eg, prostanoid receptor agonists, metabolic modulators, neurohormonal modulators, tyrosine kinase inhibitors) fit in? How can we identify subgroups of patients that respond to a specific pharmacologic pathway? Only well-designed and well-performed randomized trials will provide the answers to these questions. It is exciting to see many of these trials ongoing currently, and the months and years ahead will bring the publication of several trials that will further advance the field.

References