

Combination Therapy in Pulmonary Arterial Hypertension (PAH): What We Know and What We Do Not Know

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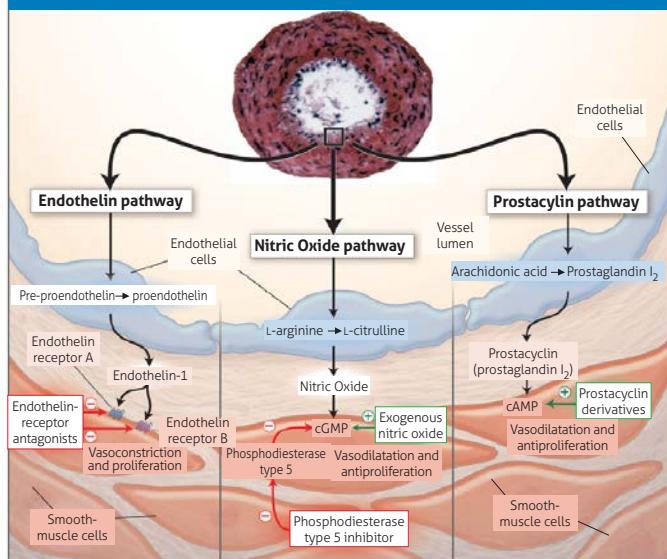
Pulmonary arterial hypertension (PAH) is a rare subtype of pulmonary hypertension characterized by proliferative vasculopathy of the small pulmonary arteries leading to increased pulmonary vascular resistance (PVR) and ultimately to right ventricular failure and death.¹ Endothelial dysfunction in the pulmonary vascular bed is thought to trigger development of PAH. Increased levels of plasma endothelin, along with lower levels of nitric oxide and prostacyclin, are implicated in PAH pathogenesis.² Currently there are three targeted pathways with five approved classes of drugs to treat PAH — endothelin receptor antagonists,

phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues and prostacyclin receptor agonists. The potential interaction between these three pathways may improve treatment outcomes, as seen in other disease states, such as hypertension, diabetes and oncology.³ (See Figure 1.) Combination therapy that targets the different PAH pathways is an attractive therapeutic option.²

PAH is a rare disease with an annual U.S. incidence of 2.3 and prevalence of 12.4 cases per million.⁴ Recent estimates from the REVEAL Registry (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) indicate a median survival of >7 years following diagnosis for patients receiving specific PAH treatment and a one-year incident mortality rate of 15 percent.⁵

Patients have been treated with PAH-specific drugs since epoprostenol (Flolan) was approved in 1995. For many years, monotherapy was the standard of care, although physicians used sequential combination therapy, ahead of trial evidence, when patients failed to achieve satisfactory results. In the early 2000s, the Hanover algorithm proposed sequential combination therapy (bosentan, add sildenafil, add inhaled iloprost, and transition to IV iloprost) when treatment goals were not met.⁶ Subsequently guidelines, clinical trials and expert algorithms provided support for combination therapy. While combination therapy has arguably become the new standard of care,⁷ gaps in knowledge of combination therapy remain. It is unclear whether initial or sequential combination therapy is better. This article is directed to managed care audiences, those making formulary decisions to optimize care of patient populations while managing health care resources, and will describe what is and what is still not known about combination therapy in PAH.

Figure 1. Targets for Current or Emerging Therapies in PAH²⁷



Clinical Trial Evidence

The first trial using initial combination therapy, BREATHE-2 (2003), assessed the safety and efficacy of bosentan in combination with epoprostenol in 33 WHO Functional Class (FC) III and IV patients.⁸ Although the trial was not positive, there was a trend toward improvement in hemodynamic parameters. Three bosentan deaths were reported, reflecting the severity of the disease. The STEP trial was conducted to assess the safety of adding an ERA (bosentan) to a prostacyclin (iloprost); efficacy was the secondary endpoint. In the 12-week trial, there was a numerically greater 6-minute walk distance (6MWD) in the combination versus the bosentan-only group. Safety data was consistent with previous trials, and comparable efficacy (TTCW [time to clinical worsening], FC and hemodynamics) was shown. As newer therapies were approved, several pivotal trials included patients on existing PAH background therapy. In the EARLY trial, bosentan was studied only in FC II patients, with approximately one-fifth of patients on stable doses of sildenafil. At month 6, geometric mean pulmonary vascular resistance (PVR) demonstrated a treatment effect of 22.5 percent ($p<0.0001$); however, the treatment effect on 6MWD was not statistically significant (19.1 m; $p=0.0758$). No individual serious adverse events were reported.⁹

In the PHIRST trial, treatment-naïve or background bosentan plus tadalafil or placebo patients were studied. At week 16 in treatment-naïve patients, tadalafil 40 mg improved placebo-adjusted 6MWD by 44 m ($p<.01$). Commonly reported mild to moderate adverse events were headache, myalgia and flushing, with similar discontinuation rates across all treatment groups.¹⁰

In TRIUMPH, inhaled treprostinil was studied in patients treated with bosentan (70 percent) or sildenafil (30 percent) or placebo. Overall there was an improvement of approximately 20 m in the 6MWD ($p=.0004$) driven by an increase in 6MWD (25 m; $p<0.0002$) for the bosentan background group. Results for the sildenafil background group were nonsignificant (9 m). The most common side effect was cough, and 11 treprostinil patients experienced a serious adverse event (AE).¹¹

PACES was the first study of significant size ($n=267$) that addressed combination therapy, adding sildenafil 80 mg three times daily (TID) (four times the approved dose) to long-term intravenous (IV) epoprostenol in patients. There was a statistically significant placebo corrected increase in 6MWD (28.8 m; $p=.001$), and improvements were seen in hemodynamic parameters (mPAP and CO), TTCW and quality of life (QoL). Headache and dyspepsia were AEs observed more often in sildenafil-treated patients.¹² More recently (2013), the PATENT-1 trial ($n=444$) investigated the safety and efficacy of riociguat in both monotherapy and combination therapy. The 12-week trial included 222 patients (194 patients on an ERA and 28 on a nonintravenous prostanoid). Riociguat demonstrated efficacy in monotherapy and combination therapy (improvement in 6MWD, PVR, NTpro-BNP, WHO FC, TTCW, QoL and Borg dyspnea score). The most common AEs were headache, dyspepsia and peripheral edema.¹³

While a number of trials using combination therapy have demonstrated positive results, the FREEDOM-C and FREEDOM-C2 trials did not demonstrate such efficacy. The FREEDOM-C study investigated the effect of adding oral treprostinil to the treatment regimen of 350 patients receiving either ERA and/or PDE5 inhibitors. At 16 weeks, the primary endpoint, improvement in 6MWD, did not reach statistical significance. A number of AEs resulted in discontinuing study drugs, including headache, nausea, diarrhea, vomiting, worsening PH, extremity pain, chest discomfort and myalgia.¹⁴

Historically, change in 6MWD has been the most frequently used primary endpoint in randomized, controlled trials (RCTs) with PAH patients. Studies suggest, however, that the 6MWD has only modest validity as a surrogate endpoint for clinical events.¹⁵ Supported by expert recommendations, recent pivotal trials for new PAH drugs have moved from short-term trials with a functional endpoint to longer, larger, event-driven trials with a composite morbidity/mortality (M/M) endpoint. In the proceedings of the fifth WSPH, TTCW was advocated as an appropriate endpoint in pivotal trials. The experts proposed a group of clinical endpoints, including all-cause death, lung transplantation, hospitalization for worsening PAH (including atrial septostomy), initiation of IV therapy due to worsening of PAH, worsening of function (measured by worsening FC and exercise capacity) and worsening of PAH symptoms (dyspnea, chest pain, dizziness/syncope and fatigue/activity level).¹⁶

Several studies using sequential combination therapy in event-driven M/M trials have been done. Although these trials have been largely positive, this is not uniformly true. For example, COMPASS-2, utilizing a composite M/M primary endpoint, evaluated sequential therapy with sildenafil and bosentan.¹⁷ The long-term (median 22.7 months) trial failed to demonstrate positive results for the primary endpoint, as the observed risk reduction of a M/M event for bosentan (added to sildenafil) versus placebo was not statistically significant. No new safety signals occurred.¹⁷

SERAPHIN was the first placebo-controlled, long-term, event-driven trial for drug registration. In SERAPHIN, macitentan was studied in patients already on PAH-specific therapy (PDE5i or nonparenteral PGI2) and in monotherapy patients using a combined M/M endpoint. There was a statistically significant 45 percent reduction ($p<0.001$) in the risk of the combined endpoint for patients treated with macitentan 10 mg versus placebo patients, which was driven by deterioration in PAH. Macitentan also reduced the risk of the combined endpoint of PAH-related death or hospitalization. Risk reduction was consistent in monotherapy and combination therapy and in both incident and prevalent patients. Adverse events occurring more frequently with macitentan than with placebo included headache, nasopharyngitis and anemia.¹⁸

In the GRIPHON trial, the novel prostacyclin IP receptor agonist — selexipag — was studied in a long-term, event-driven, placebo-controlled trial using a composite M/M endpoint.¹⁹ At the time of randomization, 80 percent of the patients were on an ERA or a PDE5i while nearly one-third of patients were on both an ERA and a PDE5i. Selexipag

reduced the risk of the composite endpoint by 40 percent ($p<0.001$), without regard to whether the patient was on monotherapy or combination therapy with two or three PAH-specific agents. The risk reduction was driven by PAH deterioration and a decrease in hospitalization. The most common AEs in the selexipag group were consistent with known prostacyclin side effects (headache, diarrhea, nausea and jaw pain).¹⁹ This trial was unique because this was the first RCT that demonstrated efficacy with triple therapy.

In the AMBITION trial, ambrisentan was studied in initial combination therapy with tadalafil (both drugs were up-titrated over an eight-week period) versus ambrisentan or tadalafil monotherapy. For the primary analysis, both groups were combined as pooled monotherapy. This was a long-term, event-driven trial with clinical failure as the primary endpoint. No placebo group was included in the study. The risk reduction for the primary endpoint in the ambrisentan/tadalafil combination-therapy group versus the pooled-monotherapy group was 50 percent ($p<0.001$). Adverse events occurring more frequently in the combination-therapy group than in either monotherapy group included peripheral edema, headache, nasal congestion and anemia. This trial was unique in that it was a treatment strategy trial and only incident patients were studied.²⁰ Results from this trial contributed to inclusion of initial combination therapy in expert guidelines (ESC/ERS 2015) for the first time.

Meta-Analyses

Combination therapy is widely used when PAH patients have a suboptimal response to initial PAH-specific monotherapy. At present, sequential combination therapy is the most widely used clinical practice strategy. While RCTs have shown drug-specific evidence, it is interesting to address the evidence across all PAH-specific drugs through meta-analysis. Recently, Liu et al., performed the first meta-analysis that separately analyzed monotherapy and combination therapy to assess the efficacy and safety of PAH-specific therapy. Databases were searched through October 2015, with 418 records identified; 35 studies met the required criteria and were included in the meta-analysis. Compared to the control group, PAH-specific therapy was associated with significant improvement in mortality (OR: 0.71; $p<0.004$), as well as statistically significant improvements in FC, 6MWD and hemodynamics. PAH-specific therapy was associated with a higher incidence of withdrawal due to adverse effects (OR: 1.53; $p<0.00001$). Specifically for combination therapy, data was available from 15 RCTs. Combination therapy did increase 6MWD by 19.96 m ($p<0.00001$) and improve FC (OR 1.65; $p=0.002$) and was also associated with statistically significant improvements in hemodynamics, including PVR and mPAP, but was not statistically significant for CI. Combination therapy was associated with a higher incidence of withdrawal due to adverse effects (OR: 2.01; $p<0.00001$).²¹ While combination therapy was positive overall, there was no mortality benefit that may be

accounted for by the short follow-up period and small sample size. Lajoie et al., also performed a meta-analysis to assess the effects of a combination of PAH-specific therapies compared with monotherapy on predefined clinical worsening in PAH.²² Of 2017 studies that were identified (published from January 1990 to May 31, 2015), only 15 studies were included in the primary analysis. Combined therapy was associated with significant risk reduction (RR: 0.65; $p<0.00001$) for clinical worsening (17 percent - 332 of 1,940 patients) versus monotherapy (28 percent - 517 of 1,862 patients). Findings from sensitivity and subgroup analyses confirmed the result robustness and suggested that the effect of combination therapy on clinical worsening was not driven by any particular drug class, study design or patient/disease characteristics. Combination therapy was not associated with significant reductions in death and transplantation as first events. The authors stated this endpoint may be negatively impacted by the risk of other competing components of a composite endpoint assessed as a time to first event. "Because admissions to hospital, transplantations and deaths most commonly occur subsequent to symptomatic progression or admission to hospital, the use of a time-to-first-event outcome might have underestimated the treatment effect of combination therapy on these subsequent outcomes."²² Combination therapy, however, was associated with an increased risk for treatment discontinuation.

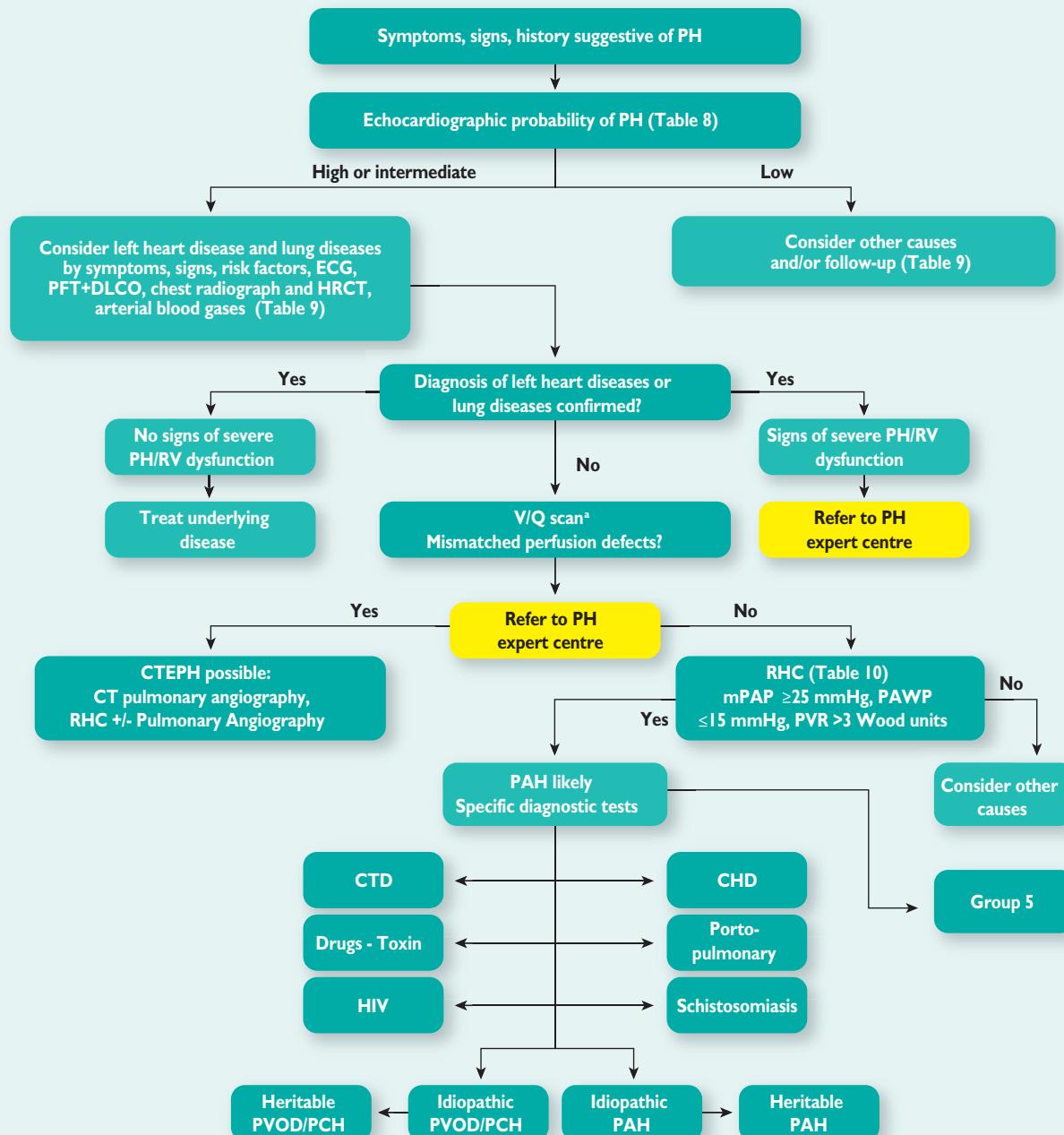
Limitations of these meta-analyses include lack of investigation of cost-effectiveness of the therapies, and these analyses did not separately evaluate the effect of sequential versus initial combination therapy. Therefore, no information was provided on whether sequential combination or initial combination offers a more beneficial outcome.

Expert Guidelines/Algorithms

For more than a decade, experts have included combination therapy within treatment algorithms as a therapeutic consideration. In the Third World Symposium on PH proceedings, held in 2003 in Venice, an algorithm was presented for NYHA FC III or IV patients. (At this time, very little information was available for patients in FC I or II.) Even though data was limited and uncontrolled, the proceedings recommended that combination therapy be considered for patients who do not show improvement or deteriorate with first-line therapy.²³

By the time the Fourth World Symposium on PH proceedings was held in Dana Point, California, in 2008, a number of clinical trials had been done that included combination therapy. These studies supported the efficacy of combination treatment for those patients still symptomatic on monotherapy. Barst et al., stated that the optimal combination based on the overall risk-benefit considerations remained unknown. However, the algorithm included combination therapy as a consideration when treatment goals were not met on

Figure 2: 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension



CHD = congenital heart diseases; CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

^aCT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

monotherapy.²⁴ Even though many health care providers had been using combination therapy for a period of time, effectively, the Dana Point algorithm moved combination therapy into mainstream treatment. Now managed care plans that had not previously paid for combination therapy began to "cover" sequential combination therapy for patients who worsened or did not improve on monotherapy. In 2013, when the Fifth World Symposium on PH proceedings was held in Nice, the experts reinforced the place of combination therapy as an option when the patient failed to reach clinical goals on monotherapy.

The most recent (2015) European Society of Cardiology/European Respiratory Society guidelines provided not only an updated algorithm but also a risk-based assessment strategy to guide therapeutic considerations. Low-risk patients have a one-year mortality risk <5 percent. These patients present with nonprogressive disease (FC I or II) with a 6MWD 440 m and no signs of clinically relevant RV dysfunction. Patients with intermediate mortality risk (5 to 10 percent) are typically in FC III with moderately impaired exercise capacity and signs of RV dysfunction. High-risk patients with mortality risk >10 percent in one year present in FC III or IV with progressive disease, including signs of severe RV dysfunction or failure and secondary organ dysfunction. The main treatment goal is reaching and maintaining a low-risk profile.

For low- or intermediate-risk patients (FC II and III — although some FC III patients may be high risk), the recommendation is for initial monotherapy or combination therapy. For high-risk patients, initial double or triple combination treatment including an intravenous (IV) prostacyclin analogue is recommended. IV prostacyclin use is mandatory for these high-risk patients because it is the only treatment that has shown a survival benefit in patients with severe disease. Recommended for initial combination therapy in incident (newly diagnosed) patients, ambrisentan/tadalafil is the only specific combination studied. For sequential combination therapy, the following drugs are recommended based on clinical evidence: macitentan added to sildenafil; riociguat added to bosentan; and selexipag added to an ERA and/or a PDE5i.

For monotherapy, since no head-to-head comparisons have been done, no evidence-based first-line monotherapy is recommended. Choice of drug depends on physician experience and preference, route of administration, side effect profile, background therapies, patient preferences, comorbidities and cost. Burger et al, in a recent real-world study, revealed 95 percent of PAH patients began with monotherapy.²⁵ When clinical response to initial combination therapy or initial monotherapy is inadequate, sequential double or triple combination therapy is recommended. Currently, sequential combination therapy is the usual practice.

Discussion

Combination therapy in PAH is an important treatment modality and is the current standard of care for most patients with PAH. With three pathways, targeting two or more of these pathways can provide an additive effect. Both clinical trial evidence and meta-analyses demonstrate benefit on morbidity, functional parameters (6MWD, FC) and hemodynamics with combination

therapy. Expert guidelines, both the Nice (2013) and the ESC/ERS (2015), have provided guidance on the place of combination therapy.

However, knowledge gaps remain. For example, how is initial combination therapy defined? Rarely in PAH are two drugs initiated at the same exact time. Is there a "best" combination?

At first glance, AMBITION trial results would lead one to believe that all patients should start with combination therapy, but the evidence is in a specific subset of patients — treatment-naïve patients — and the AMBITION trial is only specific to the ambrisentan/tadalafil combination. Further, edema occurred in almost one of every two ambrisentan/tadalafil patients, which, in clinical practice, necessitates additional clinical evaluation and intervention or discontinuation of one or more of the agents. Many patients who present at an expert center may have been seen by one or more physicians and treated with PAH-specific therapy.²⁶ The evidence from AMBITION does not provide any data to tell us if initial combination therapy demonstrates superior outcomes for prevalent PAH patients, who make up the bulk of patients in any managed care plan.

Although both the SERAPHIN and GRIPHON trials provide important results for incident and prevalent patients, neither of these trials was designed to reveal which specific combination of therapy works best. In a retrospective analysis of real-world clinical data on newly diagnosed PAH patients from Sitbon et al., looking at ERA (ambrisentan, bosentan) + PDE5i (sildenafil, tadalafil) combination therapies, none of the four ERA-PDE-5i combinations was superior.² Tadalafil compared to sildenafil may have performed better in regard to improving hemodynamics, but maximum effective dose, persistency and compliance may have contributed to this difference. Persistency and compliance with combination therapy is another issue that has not been clarified. Two recent meta-analyses (Liu and Lajoie) revealed withdrawal and treatment discontinuation were more likely to occur in patients receiving combination therapy.^{21,22}

From a pharmacoeconomic perspective, initial combination therapy is expensive for both patients and managed care organizations. When the AMBITION trial's Kaplan-Meier curves are examined, the biggest step-down occurred at six months for both the combination and the pooled monotherapy arms. This marks the first time that patients could meet the unsatisfactory clinical response component of the composite endpoint. There was no difference between the two groups for this component. Many of these events were hospitalizations, calling into question the cost benefit of up-front combination therapy in the first six months. In long-term, event-driven trials, such as SERAPHIN and GRIPHON, reduction in hospitalizations was beneficial not only in combination but also in monotherapy on macitentan and selexipag, respectively. Lastly, the risk stratification approach from ESC/ERS is an attractive alternative. Using this algorithm, the decision when to use combination therapy is left to the provider and patient. Expert guidelines suggest the patient be reassessed as early as three months, and if goals are not met, adding a second drug at that time. Such patient-tailored therapy may be not only efficacious but also safe and cost-effective. Knowledge gaps on combination therapy still exist. Further research, including real-world studies, is warranted to close these knowledge gaps.

PAH Oral Medications With Pivotal Trials

| Study | Drug | Duration | Primary Endpoint | Number of Patients |
|-------------------------|-----------------------|------------|---------------------------------|--------------------------|
| Study-351 ²⁸ | bosentan | 12 weeks | 6MWD | 32 |
| BREATHE-1 ²⁸ | bosentan | 16 weeks | 6MWD | 213 |
| EARLY ²⁸ | bosentan | 24 weeks | PVR, 6MWD | 185 |
| ARIES-1 ²⁸ | ambrisentan | 12 weeks | 6MWD | 202 |
| ARIES-2 ²⁸ | ambrisentan | 12 weeks | 6MWD | 192 |
| SUPER-1 ²⁸ | sildenafil | 12 weeks | 6MWD | 277 |
| PHIRST ²⁸ | tadalafil | 16 weeks | 6MWD | 405 |
| SERAPHIN ²⁸ | macitentan | 115 weeks* | Time to first M/M event | 742 |
| FREEDOM-M ²⁸ | oral trep | 12 weeks | 6MWD | 228 ⁺ |
| GRIPHON ²⁸ | selexipag | 71 weeks* | Time to first M/M event | 1156 |
| AMBITION ²⁰ | Ambrisentan/tadalafil | 73 weeks | First event of clinical failure | 500 primary analysis set |
| Patent-1 ¹³ | Riociguat | 12 weeks | 6MWD | 443 |

*Median treatment period; ⁺228 = primary analysis group. N = 349; 6MWD=6-minute walk distance; PAH=pulmonary arterial hypertension; PVR=pulmonary vascular resistance.

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