**Inhaled treprostinil sodium for pulmonary hypertension**

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**Introduction:** Pulmonary arterial hypertension is an increasingly recognized heterogeneous disease with significant morbidity and mortality, requiring a multimodal approach to treatment. Inhalation administration of treprostinil sodium (Tyvaso®) permits higher local drug concentration without some of the side effects of parenteral prostanooids.

**Areas covered:** After a broad discussion centering on available prostacyclins, a thorough literature review of treprostinil is undertaken, focusing on the timeline of clinical studies, specifically highlighting the major trials that shape current indications and usage. The literature search was undertaken via multiple search engines and strategies with review of cited and associated articles to provide a comprehensive discussion on the topic.

**Expert opinion:** While safe and well tolerated, inhaled treprostinil sodium should be limited, based on available data, to use as add-on therapy for patients with Group I pulmonary hypertension not effectively controlled on oral therapy. Despite documented safety for the conversion from inhaled iloprost to inhaled treprostinil, the transition of patients stable on parenteral agents to inhaled treprostinil should be cautioned due to the potential for clinical decompensation.

**Keywords:** 6-minute walk distance, functional capacity, inhaled therapy, prostacyclin analogue, pulmonary arterial hypertension, treprostinil (sodium)

**Expert Opinion on Orphan Drugs**

1. **Background**

Pulmonary hypertension (PH) is an increasingly prevalent problem, bridging across many subspecialties of medicine. It involves a pulmonary arteriopathy (primary or secondary), which leads to elevation in pulmonary arterial pressure (PAP), and eventually, right-sided heart failure. While the initial insult is varied, the result of many different systemic conditions, the end pathway is common with pulmonary vasoconstriction and smooth muscle proliferation. Based on prevalence of underlying disease alone, the most common forms of PH originate from problems in the left heart, including heart failure (both systolic and diastolic dysfunction) and valvular heart disease as well as from lung diseases (Dana Point Group II and III, respectively) [1]. Treatment in these cases should be focused on the underlying disorder and the role of adjuvant pulmonary arterial hypertension (PAH)-targeted therapy remains controversial. When the disease process is isolated to involvement of the pulmonary arterioles and has no discernible etiology, it is referred to as ‘idiopathic’ pulmonary arterial hypertension (iPAH), previously termed ‘primary’ PAH. It is now recognized that PAH related to other disorders, including congenital heart (shunt) lesions, connective tissue disease (such as scleroderma), and human immunodeficiency virus, behaves similarly to iPAH. As a result these disorders are now organized together with iPAH into Group I of the Dana Point PH Classification Scheme (Table 1). Nearly all prior drug trials in PH have focused on Group I patients (PAH), and this will, therefore, be the main patient population referred to in this review. Although much still remains to be learned about its pathogenesis,
PAH is well accepted as a marker of poorer clinical outcomes, including right ventricular failure and death.

2. Drug classes

The development of disease-specific pharmacotherapies for PAH has focused primarily on the reversal of pulmonary vasoconstriction and the inhibition of smooth muscle proliferation. The three main targeted pathways include the inhibition of endothelin (a potent vasoconstrictor) with endothelin receptor antagonists (ERA), the potentiation of the nitric oxide (a smooth muscle relaxant) activity by inhibition of breakdown (phosphodiesterase subclass 5 [PDE-5] inhibitors) or independent stimulation of its targeted enzyme (soluble guanylate cyclase stimulators), and the administration of prostacyclin (a smooth muscle dilating prostaglandin) or

**Box 1. Drug summary.**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Treprostinil sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
</tr>
<tr>
<td>Indication</td>
<td>Pulmonary arterial hypertension (WHO Class I) with NYHA Class III symptoms to increase walk distance</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>Prostacyclin analogue</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Inhalational (also available in intravenous and subcutaneous formulations)</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>![Chemical structure image]</td>
</tr>
</tbody>
</table>

**Pivotal trial(s)**

TRIUMPH I

**Table 1. Updated Dana point classification scheme for pulmonary hypertension.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Pulmonary arterial hypertension Primary Idiopathic</td>
</tr>
<tr>
<td>Group I</td>
<td>Pulmonary vaso-occlusive disease</td>
</tr>
<tr>
<td>Group II</td>
<td>Pulmonary venous hypertension (left heart disease) Systolic dysfunction</td>
</tr>
<tr>
<td>Group III</td>
<td>PH associated with lung disease or hypoxemia Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Group IV</td>
<td>Chronic thromboembolic PH Obstruction of proximal pulmonary arteries</td>
</tr>
<tr>
<td>Group V</td>
<td>PH due to unclear multifactorial mechanisms Hematologic: myeloproliferative disorders, splenectomy, myoglobinopathy</td>
</tr>
</tbody>
</table>

PH: Pulmonary hypertension.
one of its analogues. ERAs, PDE-5 inhibitors, and soluble guanylate cyclase stimulators are available in oral formulations, while prostanoids are only approved for intravenous, subcutaneous, or inhalational administration. Studies have shown improvement in functional capacity in patients with moderate degrees of clinical impairment (WHO function class II and III) with all classes of drugs [2-11]. Most of these studies have been short (usually 12–16 weeks) in duration, with arguably softer endpoints such as 6-min walk distance (6MWD) and pulmonary vascular resistance (PVR); though a recent meta-analysis points to a possible beneficial impact on survival with oral therapies [12]. However, there is little data to support the primary use of oral agents in patients with advanced PAH (WHO Class IV). Intravenous prostacyclin or its analogues are generally recommended for these patients. Despite this fact, only a single study (using intravenous epoprostenol) has directly demonstrated mortality reduction in this patient population [13,14]. A major limitation of current knowledge is the lack of head-to-head comparison studies between drug classes; and as such, current guidelines mainly reflect on the improved side effect and delivery profiles of oral and inhalational agents for patients with less limiting disease. Conversely, combination regimens have been increasingly studied, showing increased efficacy among most drug classes and suggesting a complementary effect through the modification of multiple pathways [15-19].

3. Overview of prostacyclin analogues

Epoprostenol was the first medication approved for the treatment of PAH in 1998. In the original outcome study assessing epoprostenol, there was a reduction in mortality as well as improvement in functional capacity, hemodynamic parameters, and quality of life assessments [14]. Interestingly, this has been the only trial to demonstrate improved survival compared to placebo, and these results have not been replicated in other prostacyclin studies. Epoprostenol, in its original formulation, was not heat stable, requiring patients to carry a cooling pack for medication cassettes that needed to be prepared and changed roughly every 24 h. Epoprostenol also has a short half-life (3–6 min), which necessitates continuous intravenous infusion via an indwelling central venous catheter. Along with complications associated with central venous catheters in addition to medication-specific toxicities, there is significant morbidity with this modality.

In an effort to identify alternatives to intravenous prostacyclin with longer half-lives, treprostinil and iloprost were developed (Box 1). Treprostinil was approved for use by the FDA in 2002. Inhaled iloprost was approved in 2004, making it the third FDA-approved drug in this class (after treprostinil and epoprostenol). However, the short half-life of this agent requires frequent dosing; and continuous hemodynamic monitoring studies have suggested that the hemodynamic effects of inhaled iloprost may not be sustained to the next scheduled dosing [20].

4. Overview of treprostinil

Treprostinil is a tricyclic benzidine analogue of prostacyclin. The mechanism of action is to mimic the effect of endogenous prostacyclin I2 [21-23]. This leads to direct vasodilation of both pulmonary and systemic vascular beds. In addition, it inhibits cellular proliferation in human smooth muscle [24] and prevents platelet aggregation.

It is predominantly metabolized by the CYP2C8 isoenzyme in the liver, with a small percentage metabolized by CYP2C9 isoenzyme [25,26]. With normal liver function, it has an elimination half-life of ~4.6 h via subcutaneous injection and ~4.4 h with intravenous administration [27]. As can be expected, hepatic insufficiency can result in up to an 80% decrease in drug metabolism [28,29]. In addition to subcutaneous injection and intravenous formulations, the FDA has most recently approved an inhalation method of delivery for use.

4.1 Subcutaneous

Subcutaneous treprostinil was the first formulation approved for use in the United States (in 2002), and was the first prostacyclin analogue to be approved for delivery that did not require a central venous catheter. Simonneau and colleagues conducted the largest multicenter randomized controlled trial in 2002 [30]. This study randomized 470 patients with iPAH, PAH associated with congenital heart disease and PAH in connective tissue disease. Compared to placebo, patients receiving subcutaneous treprostinil experienced symptom reduction, as well as improved invasive hemodynamics and functional capacity as measured by 6MWD at 12 weeks. Subsequent open-labeled extensions have shown persistent benefit with up to 70% survival as far out as 4 years [31-34]. Along with medication toxicities associated with treprostinil (such as systemic hypotension, flushing, diarrhea, nausea, and vomiting), subcutaneous administration was associated with increased rates of local reactions of pain, erythema, and infections. Although techniques were developed to mitigate the discomfort induced by subcutaneous administration [35], the frequency of discontinuations due to this problem eventually led to development of alternative methods of delivery.

4.2 Intravenous

Intravenous treprostinil was approved in 2004 by the FDA, largely based on bioequivalence data to subcutaneous treprostinil. Tapson and colleagues conducted an open-label randomized controlled trial in patients with WHO function class III–IV PAH [36]. Patients receiving treprostinil experienced an improvement in hemodynamics and functional capacity including a mean 80 m increase in 6MWD. The TRUST study group subsequently confirmed these results, where treprostinil patients experienced improvements in hemodynamics, functional capacity, symptoms, and surrogate biomarkers [37]. It is important to note the ethical concerns...
sparked by performing a placebo-controlled trial in advanced PAH, where the evidence base for therapy was already strong at the time of initiation [38].

Given the progressive nature of PAH, there is always the potential need to switch within and between drug classes. A study of 27 patients, who were switched from intravenous epoprostenol to intravenous treprostinil, showed maintenance of exercise capacity and WHO functional class [39]. However, there was an observed increase in mean pulmonary artery pressure and decrease in cardiac index.

4.3 Oral
Oral treprostinil has been used in Europe under orphan medicinal product status, but is currently awaiting approval by the FDA in the United States. The initial studies, FREEDOM-C and FREEDOM-C2, were done as add-on therapies to primarily bosentan and sildenafil [40,41]. In these trials, there was no improvement in functional capacity when compared to monotherapy alone. Presumably, it is this lack of efficacy in the initial studies that initially prompted the FDA to withhold approval. However, a monotherapy study, FREEDOM-M, has since been completed, demonstrating improvement in functional capacity with oral treprostinil over placebo [42]. A summary of the different formulations and major trials for treprostinil are summarized in Table 2.

5. Inhaled treprostinil

5.1 Pharmacokinetics
As previously mentioned, treprostinil is hepatically metabo-

ized and metabolism is decreased in hepatic insufficiency.
In healthy patients, inhaled treprostinil (Tyvaso®) has been
to have a bioavailability of 64 – 72% with a dose-
related increase in bioavailability [43]. In the same Phase I single dose escalation study, the maximum tolerated dose was 84 µg. On the basis of these findings, the FDA has recommended a target human dose of 54 µg.

Most of the elimination data has come from intravenous and subcutaneous treprostinil studies. In comparison to intravenous and subcutaneous formulations, inhaled treprostinil is eliminated similarly. The measureable plasma half-life is approximately 44 – 52 min [44]. The terminal half-life of treprostinil based on subcutaneous administration is ~ 2.6 – 4.6 h [29]. The peak effect is 18 ± 2 min, which correlates to peak plasma concentration of ~ 10 – 15 min [45]. Interestingly, while the peak effect is < 20 min, the reductions in PVR can be seen for > 3 h after the dose.

Given that inhaled treprostinil was the second inhaled pros-
tacyclin analogue to be approved, it is important to understand the pharmacokinetics in relation to inhaled iloprost. Inhaled treprostinil has a later peak effect (18 ± 2 compared to 8 ± 1 min for inhaled iloprost); and while they both result in similar reductions in PVR, the effect of inhaled treprostinil is seen for significantly longer (> 3 h after the dose) [45]. The peak effect correlates with peak plasma concentrations (10 – 15 min of peak plasma concentration with a peak effect between 16 – 20 min), whereas the hemodynamic effects persist even after trough plasma levels. This correlates to the dosing schedule of inhaled iloprost of 6 – 9 times daily compared to 4 times daily for inhaled treprostinil.

5.2 Mode of delivery
The FDA approval for inhaled treprostinil was specifically for the Tyvaso Inhalation System, an ultrasonic nebulizer that delivers medication via a pulsed delivery device. While the device has been modified several times, the complexity of its technology still limits mobility. There has not been a metered dose inhaler (MDI) device approved for PAH, even though its use as an inhalational delivery method is pervasive in other pulmonary pathologies. Voswinckel and colleagues looked at the clinical efficacy of inhaled treprostinil delivered via an MDI compared to inhaled nitric oxide [46]. After baseline hemodynamic parameters were acquired, patients received 20 PPM of inhaled nitric oxide with direct measurement of these same measurements. After a washout period, patients received different dosages of inhaled treprostinil via MDI (30, 45, 60 µg) with continued monitoring for 2 h. Patients showed sustained improvement in PAP, PVR, and cardiac output (CO). Notably, all of these dosages showed improvement compared to placebo. The authors also compared MDI-delivered inhaled treprostinil to historical cohorts at their institution, and showed comparable reductions in PVR; however, they noted that direct comparisons could not be made. Notably, the hemodynamic effects of inhaled treprostinil via a MDI were seen within seconds of dosage administration.

### Table 2. Treprostinil sodium – formulations and landmark trials.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Landmark trial</th>
<th>Approved in US</th>
<th>Year approved</th>
<th>Approved in Europe</th>
</tr>
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<tr>
<td>Intravenous</td>
<td>Tapson et al. 2006 [36]</td>
<td>Yes</td>
<td>2004</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral</td>
<td>FREEDOM-C</td>
<td>No</td>
<td>N/A</td>
<td>Orphan drug status</td>
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<td></td>
<td>FREEDOM-C2</td>
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<td></td>
<td>FREEDOM-M</td>
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<tr>
<td>Inhalational</td>
<td>TRIUMPH I</td>
<td>Yes</td>
<td>2009</td>
<td>Orphan drug status</td>
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</table>
5.3 Clinical efficacy
The initial study of inhaled treprostinil was performed in three European patients with severe PAH, each of who received a single dose of 15 µg [47]. These patients experienced an average 45% decrease in PVR. Two of these patients were continued on inhaled treprostinil for long term and were noted to have an improvement in function class and 6MWD at 3 months.

This small study was followed very shortly by a larger, three-armed study [45]. While the second and third arms mainly assessed the pharmacodynamics and pharmacokinetics of inhaled treprostinil, the first arm was a randomized, open-label, single-blind crossover study of 44 patients with moderate to severe PAH. Patients predominantly had iPAH, but the study also included other assorted Dana Point Group I PAH, as well as chronic thromboembolic PH. Patients were randomized to either inhaled iloprost or treprostinil and then crossed over to the other agent after a 1 h washout period. The iloprost dose was fixed, while treprostinil doses included 4, 8, or 16 µg/ml. Similar reductions in PVR were seen with both drugs, though the effect was longer lasting in the treprostinil group (> 3 vs < 1 h). Differences in safety profile were suggested, with systemic hypotension occurring with iloprost, which was not witnessed with treprostinil.

In the next major study, Channick and colleagues examined 12 patients with iPAH or PAH associated with connective tissue disorders, who had WHO function class III–VI symptoms despite at least 12 weeks of bosentan [44]. In this open-label safety and efficacy trial, patients were administered either 30 or 45 µg of inhaled treprostinil, with significant improvements in hemodynamics (mean pulmonary artery pressure) and functional parameters (6MWD and WHO function class) noted with both doses.

Voswinckel and colleagues performed an open-label safety and efficacy trial in 50 patients with moderate to severe PAH, either idiopathic or associated with chronic thromboembolic disease, who experienced acute vasoreactivity during inhalation of nitric oxide [48]. Patients were administered 50 mg of sildenafil orally and then randomized to either 15 or 30 µg of inhaled treprostinil. An additive decrease in PVR and mean pulmonary artery pressure was seen, along with a trend toward improved CO.

These studies led to the pivotal, Phase III clinical trial that shaped the FDA approval of inhaled treprostinil, TRIUMPH I. TRIUMPH I was a 12-week randomized, placebo-controlled, double-blind multicenter trial involving 235 patients with Group I PAH and WHO function class III–IV already taking bosentan or sildenafil [49]. Modest, but statistically significant, improvements were seen in 6MWD, facets of the quality-of-life questionnaire as well as NT-pro-BNP levels, though there were no improvements noted in Borg Dyspnea Score, WHO function class, symptoms, time to clinical worsening, or survival. A subsequent open-label extension of the study suggested benefits that were sustained to as far as 2 years [50]. While the average difference in improvement between the treatment group and placebo group in 6MWD was only 20 m, improvement of > 50 m was observed in over 30% of patients in the inhaled treprostinil group, compared to 12% in the placebo group.

5.4 Safety
Inhaled treprostinil appears to have a better safety profile than systemic prostanoids. The most commonly reported side effects are transient cough – noted in 10 – 54% of patients [44,48,50] and headache – noted in up to 42% of patients [49,50]. Flushing [49] and vomiting [50] were also seen, though not consistently in all studies. Other side effects typically associated with systemic administration of prostanoids, such as diarrhea, hypotension, or bradycardia, did not differ from placebo.

5.5 Crossover effectiveness
Since inhaled treprostinil’s approval, there have been a few studies examining the safety and efficacy of transitioning from other prostanoids to treprostinil. One study examined transition from systemic prostacyclin analogues to inhaled treprostinil and showed stability in hemodynamic parameters and 6MWD, though a small number of patients developed worsening of WHO function class [51]. Patients transitioned from inhaled iloprost to inhaled treprostinil, however, showed no worsening of hemodynamic parameters, 6MWD or WHO function class [52].

6. Conclusion
Treprostinil, a prostacyclin analogue, was first introduced into the United States a little over a decade ago and the agent is most remarkable for the multiple methods of administration that have been developed over this time. The ability to deliver medication through inhalational means is particularly attractive in PAH because of the capability of achieving higher local concentrations of active medication while avoiding systemic side effects. With the backdrop of data demonstrating the safety and efficacy of subcutaneous and intravenous treprostinil, inhaled treprostinil has shown, through most Phase I and II studies, equivalence in most pharmacologic parameters. Dosing and administration has been a major challenge for other inhaled agents, and has unfortunately limited their clinical use. Given its relatively long half-life, delayed peak effect, and prolonged physiologic effects, treprostinil has a potential edge over other prostacyclin analogues. Unfortunately, the exclusive hepatic clearance of treprostinil does increase the potential for drug-drug interactions, though no major issues have been reported to date.

The safety profile of inhaled treprostinil appears very favorable, even compared to other systemic prostanoids including treprostinil. While the incidence of side effects is significant (upward of 40 – 50%), most are mild in severity. Those most commonly witnessed include transient cough and
headache, with neither being treatment limiting. Interestingly, many side effects associated with systemic prostanoid administration that can lead to treatment discontinuation, such as diarrhea, hypotension, and bradycardia, are not seen with inhalation of treprostinil.

Clinical effectiveness data for inhaled treprostinil mainly comes from add-on and conversion studies. TRIUMPH I, the only large placebo-controlled trial with inhaled treprostinil published to date, demonstrated improved hemodynamics, quality-of-life measures, and treatment satisfaction, but no statistically significant improvement in function class or time to clinical worsening [53]. An additional limitation of the supportive data for inhaled treprostinil (as with many PAH drugs) is the lack of comparator studies. Only a single study matched inhaled treprostinil against its major competitor, iloprost, and showed similar, though more prolonged, reduction in PVR. Crossover data further suggest that not only is there no difference in short-term efficacy, but also that inhaled treprostinil is equally well tolerated in those previously treated with iloprost, with only 4% of patients discontinuing inhaled treprostinil due to an adverse event [52]. Worsening in function class in some patients converted from intravenous prostanoid to inhaled treprostinil suggests that inhalational administration is not interchangeable with intravenous drugs, and that intravenous prostanoids should remain the gold standard therapy for patient with advanced symptoms.

There is very little data examining inhaled treprostinil as first-line therapy, particularly in patients with less severe functional impairment. First-line, guideline-based therapy for patients with PAH and function class II and III begins with oral agents, which were given the highest level of supportive evidence in the European Guidelines [54]. Iloprost has been approved for function class III patients with A-level appraisal of the evidence per the European guidelines. Iloprost was also FDA approved for use in function class IV patients, though the European guidelines gave it a IIa-C recommendation, similar to agents other than epoprostenol.

The European guidelines gave inhaled treprostinil an I-B recommendation for function class III patients and a IIa-C recommendation for function class IV. The American societies last released an expert consensus document in 2009, prior to the FDA approval of inhaled treprostinil. As such, they did not make recommendations or specify the indications for inhaled treprostinil [55]. The FDA has approved inhaled treprostinil in the US for function class 3 patients with PAH.

7. Expert opinion

The potential applications for inhaled treprostinil based on its safety profile and patient tolerability would initially appear to be quite broad, though further examination of the clinical efficacy data dampens such enthusiasm. TRIUMPH I, the only large randomized placebo-controlled study of inhaled treprostinil, found no statistically significant improvements in function class or time to clinical worsening, arguably the most important clinical endpoints examined in the study. Although improvement in functional capacity was noted in multiple smaller studies, none were as rigorously performed as TRIUMPH. Also as noted earlier, only a single study compared treprostinil to iloprost, its major competitor in the PAH market. Although the magnitude of acute effect on PVR was found to be similar, the authors lauded the prolonged duration of action. Presumably, more frequent dosing with iloprost (as is currently recommended) would overcome such a discrepancy.

It is also important to note that the largest Phase III study of iloprost (203 patients with WHO function class III and IV) showed statistically significant improvements in hemodynamics, time to clinical worsening, function class, and quality of life when compared to placebo in previously untreated patients [56]. Although TRIUMPH I was at a disadvantage coming later in time (when administering solely placebo to patients with PAH and advanced symptoms would be considered unethical) and despite the inaccuracy and biases generated by comparing different studies performed during different time periods, the differing outcomes in these two studies is still concerning.

The FDA indications for inhaled treprostinil appear to be appropriately limited in scope given prior study results and the quality of the data. Therapy should not be extended beyond patients in Dana Point Group I, as there is little data to support such use. Also patients should have moderately severe functional limitation (WHO function class III) at the time of therapy initiation. However, the recommendations still leave some uncertainty about whether certain subsets of patients should be initiated on inhaled treprostinil, particularly drug naïve patients. Inhaled treprostinil has only been investigated as add-on therapy, though this is not overtly mentioned in the indications. While there may still be a role for it as a first-line agent, particularly given the excellent safety profile, disease progression can occur in some patients during therapy and it is our belief that patients receiving this agent as monotherapy should be reassessed in timely fashion, with therapy added or escalated as necessary. Physicians should also resist the temptation to switch patients from intravenous to inhalational prostanoid therapy when the disease appears to have stabilized because of the risk for decompensation. In patients who are failing oral therapy and are resistant to initiation of an intravenous prostanoid, however, starting inhaled treprostinil seems most reasonable.

The prolonged therapeutic effect and the reduced frequency of administration makes inhaled treprostinil a more attractive option compared to inhaled iloprost. However, patients should be appropriately informed about the lack of comparative data, and that clinical outcomes may not be equivalent with both agents. Until further comparative data emerge, use of inhaled treprostinil should remain limited to add-on therapy for patients with Group I PAH, who are
already taking oral therapy and in WHO function class III, with the expectation of improving hemodynamics and 6MWD. As such it is a very important addition to our pharmacological armamentarium for this devastating disorder. Further studies should examine whether patients with less symptomatic impairment or etiologies of PH outside of Group I also benefit from inhaled treprostinil.

**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.


**The first study (single center involving 162 patients and compared to historical controls) to demonstrate a mortality benefit in patients with idiopathic pulmonary arterial hypertension.**


**Multicenter randomized trial which found that IV epoprostenol led to improved echocardiographic indices of right ventricular function and an important surrogate of mortality that was subsequently neglected until only recently.**


**Declaration of interest**

RA Krasuski is a consultant for Actelion and on the speakers bureau of Actelion and Bayer and on the scientific advisory board for VentriPoint Diagnostics Ltd. V Gupta has no conflict of interest. The authors received no payment in preparation of this manuscript.
interaction potential with treprostinil. Am J Respir Crit Care Med 2009;179:A3567
• A combined analysis of three placebo-controlled trials which demonstrated improved survival compared to what was expected without therapy for PAH patients receiving subcutaneous treprostinil.
• A nice review of subcutaneous treprostinil with a large focus on management strategies to reduce infusion site pain.
• This study provided the pharmacokinetic data that determined the current dosage and frequency of administration for inhaled treprostinil.
• A prospective study of 12 patients, who were symptomatic on bosentan and received inhaled treprostinil with improvements in hemodynamics and functional capacity.
** Randomized placebo-controlled trial of inhaled treprostinil in 235 patients with Class III or IV symptoms and reduced walk distance which demonstrated an improvement in walk distance and quality of life but not for clinical worsening.
Management of Pulmonary arterial Hypertension (TRIUMPH) study open-label extension. J Heart Lung Transplant 2011;30(12):1327-33

• An open-label continuation of the TRIUMPH study, in which patients had sustained benefits of inhaled treprostinil for up to 2 years after initiation.


• Provides the foundations for current evaluation, diagnosis, and management of patients with pulmonary hypertension.


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