# An observational study of inhaled-treprostinil respiratory-related safety in patients with pulmonary arterial hypertension

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**Abstract:** Inhaled treprostinil (Tyvaso) has been shown to be a safe and effective addition to pulmonary arterial hypertension (PAH) oral therapies; however, the respiratory-related safety profile of inhaled treprostinil required further elucidation in the setting of routine clinical care. The objectives of this study were to characterize respiratory-related adverse events (AEs) associated with current or recent treatment with inhaled treprostinil and to compare the incidence of respiratory-related AEs in PAH patients treated with inhaled treprostinil with that in patients treated with other Food and Drug Administration (FDA)–approved PAH therapies. This was a long-term, prospective, observational study. All respiratory-related AEs were recorded during the study. The number of PAH patients enrolled was 1,333, 666 treated with inhaled treprostinil and 667 controls (treated with an FDA-approved PAH therapy other than inhaled treprostinil), for a total of 958 and 1,094 patient-years of exposure, respectively. In the inhaled-treprostinil group, 1,281 respiratory-related AEs were reported in 403 patients (61%), and in the control group, 1,295 respiratory-related AEs were reported in 388 patients (58%). Cough, throat irritation, nasal discomfort, and hemoptysis were the most common respiratory-related AEs (occurring in ≥2% of patients in either treatment group) that demonstrated a higher number of events per patient-year of exposure in the inhaled-treprostinil group than in the control group (risk ratio [95% confidence interval]: 1.487 [1.172–1.887], 3.777 [2.050–6.956], 2.039 [1.072–3.879], and 1.957 [1.024–3.741], respectively). Overall, inhaled treprostinil was well tolerated by PAH patients in routine clinical care, with respiratory-related AEs consistent with the known safety profile (trial registration: clinicaltrials.gov identifier: NCT01266265).

**Keywords:** prostacyclin, adverse events, tolerability.

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Pulmonary arterial hypertension (PAH) is a rare, progressive, hemodynamic disorder characterized by abnormally high pressure in the pulmonary arteries due to elevated pulmonary vascular resistance.[1] There are five major classes of PAH-specific drugs: endothelin receptor antagonists (ERAs; bosentan, ambrisentan, macitentan), phosphodiesterase type 5 inhibitors (PDE5Is; sildenafil, tadalafil), soluble guanylate cyclase stimulators (sGCs; riociguat), prostacyclins (epoprostenol, treprostinil, iloprost), and prostacyclin receptor agonists (selexipag).[2,3] ERAs and PDE5Is are typically used in patients with less severe functional impairment, whereas prostacyclin therapy is generally reserved for more advanced PAH.[4,5] Originally available only for parenteral use, prostacyclins are now formulated for inhalation or oral administration, allowing for optimized PAH management.[3]

Tyvaso (treprostinil sodium for inhalation), an inhaled prostacyclin, was approved by the United States Food and Drug Administration (FDA) in 2009 for use in patients with World Health Organization (WHO) group 1 PAH to improve exercise capacity.[6] Inhaled treprostinil was developed as an alternate route of administration to reduce route-specific risks associated with parenteral administration, particularly infusion site pain and bloodstream infections. During a pivotal, placebo-controlled, phase 3 study (TRIUMPH),[7] the majority of respiratory-related adverse events (AEs) reported in patients receiving inhaled treprostinil were mild or moderate in intensity and included cough (54%), throat irritation (14%), pharyngolaryngeal pain (11%), epistaxis (5%), hemoptysis (3%), and wheezing (3%).

The purpose of our study was to further characterize the respiratory-safety profile associated with routine clinical use of inhaled treprostinil in a large, representative sample of patients with WHO group 1 PAH. The primary objective was to describe the type and incidence of respiratory-related AEs potentially associated with current or recent treatment with inhaled treprostinil for PAH. The secondary objective was to compare the incidence of respiratory-related AEs in patients treated with inhaled treprostinil with that in patients treated with other FDA-approved therapies for PAH.

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## METHODS

Patients were enrolled in this long-term, prospective, observational safety study (RIN-PH-403; clinicaltrials.gov identifier: NCT01266265) at 94 centers in the United States. Approximately 1,320 patients (660 per treatment group) were planned for enrollment to accrue 1,000 patient-years of exposure per treatment group. Eligible patients with a clinical diagnosis of WHO group 1 PAH were enrolled by their prescribing physician and assigned to a treatment group based on inhaled-treprostinil use at the time of study entry. The control group included patients receiving any FDA-approved PAH therapy other than inhaled treprostinil. The inhaled-treprostinil group consisted of patients prescribed and currently treated with inhaled treprostinil at any dose. Treprostinil was administered with the Tyvaso inhalation system (United Therapeutics, Research Triangle Park, NC). The dosage and administration schedule of all medications in both treatment groups were determined on a patient-specific basis, according to the prescribing physician's regular care practice. Patients were excluded if they had previous initiation and permanent discontinuation of inhaled treprostinil, current or past diagnosis of lung neoplasm, active gastrointestinal or pulmonary hemorrhage, or planned surgical intervention for the treatment of PAH. All patients provided written informed consent. The study was approved by the institutional review board at each site.

### Assessments

Baseline demographics, relevant medical history, PAH history, current PAH therapy, and concomitant therapies were assessed. Follow-up visits occurred approximately every 3 months from study enrollment. At follow-up visits, concomitant therapies, changes in PAH therapy, and respiratory-related AEs were reported. The preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1, were used to summarize the respiratory-related AEs. Investigators reported all respiratory-related AEs, regardless of suspected cause. AEs occurring within 30 days of therapy discontinuation were included in safety analyses. Respiratory-related AEs were also grouped into the following categories by the medical monitor (Table S1, available online): evidence of bleeding from the upper and/or lower respiratory tract; wheezing, bronchospasm, or exacerbation of preexisting asthma or chronic obstructive pulmonary disease (COPD); irritation or pain affecting the nose, mouth, larynx, or pharynx; and upper and/or lower respiratory tract infection.

### Statistical analysis

Consistent with the observational study design, no formal hypothesis testing was planned, no sample size estimations were calculated, and all results presented are descriptive. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess differences in the proportion of patients who experienced a given respiratory-related AE. Risk ratios (RRs) and 95% CIs were used to evaluate differences in the rate of events per patient-year of exposure between the inhaled-treprostinil and control groups.[8] Analyses of the differences in rates of AEs between groups were performed after AEs were grouped by category of interest and after adjustment for covariates of interest, including a history of underlying lung disease and New York Heart Association (NYHA) functional class at baseline. AEs were also evaluated by type of background PAH therapy. Statistical analyses were performed with SAS statistical software (SAS Institute, Cary, NC).

## RESULTS

### Baseline characteristics and patient disposition

Between February 2011 and December 2014, 1,333 patients were enrolled, with even distribution between the inhaled-treprostinil ($n$ = 666) and control ($n$ = 667) groups. The mean (±SD) inhaled-treprostinil exposure time during the study period was 75 ± 50.7 weeks, with a mean time receiving inhaled-treprostinil treatment at enrollment of 46 ± 49.3 weeks. The mean exposure time during the study period in the control group was 86 ± 47.8 weeks. At enrollment, 50% of the inhaled-treprostinil subjects were receiving inhaled treprostinil in combination with both an ERA and a PDE5I, as compared to inhaled treprostinil in combination with a PDE5I alone (29%), with an ERA alone (11%), with an ERA and an sCG (<1%), or as monotherapy (9%). Total inhaled-treprostinil exposure was 958 patient-years, and total control exposure was 1,094 patient-years.

Baseline demographics and characteristics are described in Table 1. The treatment groups were similar with regard to their PAH disease history but differed with regard to baseline NYHA functional classification, with a higher proportion of patients in the inhaled-treprostinil group having more severe disease (NYHA functional class 3; inhaled treprostinil: $n$ = 332 [50%]; control: $n$ = 239 [36%]). Medical history at baseline was similar between treatment groups (inhaled treprostinil; control), with the exception of cough ($n$ = 118 [18%]; $n$ = 36 [5%]), COPD ($n$ = 170 [26%]; $n$ = 126 [19%]), interstitial lung disease ($n$ = 65 [10%]; $n$ = 41 [6%]), congestive cardiac failure ($n$ = 66 [10%]; $n$ = 46 [7%]), and chronic renal failure ($n$ = 53 [8%]; $n$ = 32 [5%]), all of which were more common in the inhaled-treprostinil group than in the control group. A medical history of asthma was more common in the control group ($n$ = 121 [18%]) than in the inhaled-treprostinil group ($n$ = 91 [14%]).

Of the 1,333 patients enrolled, 295 (30%) prematurely discontinued the study (inhaled treprostinil: $n$ = 205 [31%]; control: $n$ = 190 [28%]). Reasons for premature discontinuation (inhaled treprostinil; control) included death (14%; 11%), lost to follow-up (3%; 4%), withdrawal of consent (2%; 2%), respiratory-related AEs (<1%; <1%), and other reasons (11%; 12%). Other reasons for study discontinuation included transfer of care to a new healthcare provider, stopping or changing PAH medications, and enrolling in another clinical study for reasons other than respiratory-related AEs.

### Respiratory-related AEs

Respiratory-related AEs that occurred in at least 2% of patients in either treatment group are presented in Table 2. The rate of events per patient-year of exposure (RR [95% CI]) of cough (1.487 [1.172–1.887]), throat irritation (3.777 [2.050–6.956]), nasal discomfort (2.039 [1.072–3.879]), and hemoptysis (1.957 [1.024–3.741]) was higher in the inhaled-treprostinil group; however, only throat irritation demonstrated a significant difference in the proportion of patients experiencing an event (OR [95% CI]: 3.395 [1.721–7.185]). In

Table 1. Baseline demographics and disease characteristics between treatment groups

| Baseline characteristic | Inhaled treprostinil ($N$ = 666) | Control ($N$ = 667) |
|---|---|---|
| Age, median (range), years | 57.5 (5–90) | 57.0 (3–97) |
| Sex, M/F | 147 (22)/519 (78) | 135 (20)/532 (80) |
| Race[a] | | |
| White | 483 (73) | 510 (76) |
| Black/African American | 116 (17) | 107 (16) |
| Other/race not disclosed | 42 (6) | 33 (5) |
| Asian | 21 (3) | 15 (2) |
| Native Hawaiian/Pacific Islander | 3 (<1) | 1 (<1) |
| American Indian/Alaska Native | 2 (<1) | 1 (<1) |
| Time since PAH diagnosis, median (range), years | 2.9 (0–32.0) | 2.9 (0–26.0) |
| PAH disease history[a] | | |
| Idiopathic/heritable/drug or toxin induced | 341 (51) | 389 (58) |
| Connective-tissue disease | 223 (33) | 195 (29) |
| Congenital heart disease | 55 (8) | 37 (6) |
| HIV infection/portal hypertension | 53 (8) | 55 (8) |
| Other | 9 (1) | 4 (<1) |
| NYHA functional class | | |
| 1 | 46 (7) | 70 (10) |
| 2 | 245 (37) | 329 (49) |
| 3 | 332 (50) | 239 (36) |
| 4 | 37 (6) | 24 (4) |
| Unknown/not assessed | 6 (<1) | 5 (<1) |
| Baseline PAH medication[a] | | |
| Prostanoids | | |
| Tyvaso (treprostinil) inhalation | 666 (100) | 0 (0) |
| Remodulin (treprostinil) | 2 (<1) | 150 (22) |
| Flolan (epoprostenol) | 2 (<1) | 44 (7) |
| Veletri (epoprostenol) | 0 (0) | 36 (5) |
| Ventavis (iloprost) inhalation | 0 (0) | 33 (5) |
| PDE5Is | | |
| Revatio (sildenafil citrate) | 294 (44) | 236 (35) |
| Adcirca (tadalafil) | 239 (36) | 224 (34) |
| Endothelin receptor antagonists | | |
| Letairis (ambrisentan) | 250 (38) | 200 (30) |
| Tracleer (bosentan) | 164 (25) | 203 (30) |
| Opsumit (macitentan) | 4 (<1) | 2 (<1) |
| Soluble guanylate cyclase stimulator | | |
| Adempas (riociguat) | 2 (<1) | 2 (<1) |

Note: Unless otherwise indicated, data are no. (%) of patients. NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PDE5I: phosphodiesterase type 5 inhibitor.

[a] Patients were instructed to designate all that apply.

contrast, the proportion of patients reporting asthma (OR [95% CI]: 0.362 [0.128–0.908]) and the rate of events of asthma (RR [95% CI]: 0.269 [0.127–0.570]) were higher in the control group. Among the 138 patients (21%) who discontinued inhaled treprostinil but remained enrolled, the incidence of respiratory-related AEs was higher during current inhaled-treprostinil exposure (83 events, 60% of patients) than after discontinuation of inhaled treprostinil (24 events, 17% of patients).

Table 2. Respiratory-related adverse events reported in ≥2% of patients in either treatment group

| | Inhaled treprostinil (*N* = 666; 957.9 pt-yr) | | Control (*N* = 667; 1,093.7 pt-yr) | | | | |
|---|---|---|---|---|---|---|---|
| Event | Patients, no. (%) | Events, no. (per pt-yr) | Patients, no. (%) | Events, no. (per pt-yr) | $\chi^2$ *P* value | Odds ratio (95% CI) | Risk ratio[a] (95% CI) |
| Any event | 403 (61) | 1,281 (1.337)[b] | 388 (58) | 1,295 (1.184)[b] | 0.3846 | 1.102 (0.880–1.380) | 1.129 (1.045–1.220)[b] |
| Cough | 122 (18) | 155 (0.162)[b] | 106 (16) | 119 (0.109)[b] | 0.2395 | 1.187 (0.883–1.597) | 1.487 (1.172–1.887)[b] |
| Upper respiratory tract infection | 99 (15) | 129 (0.135) | 115 (17) | 158 (0.144) | 0.2373 | 0.838 (0.618–1.136) | 0.932 (0.739–1.176) |
| Epistaxis | 89 (13) | 117 (0.122) | 80 (12) | 109 (0.100) | 0.4525 | 1.132 (0.809–1.585) | 1.226 (0.945–1.590) |
| Bronchitis | 57 (9) | 75 (0.078) | 56 (8) | 73 (0.067) | 0.9151 | 1.021 (0.681–1.531) | 1.173 (0.851–1.617) |
| Dyspnea | 55 (8) | 63 (0.066) | 66 (10) | 85 (0.078) | 0.2983 | 0.820 (0.552–1.213) | 0.846 (0.612–1.171) |
| Pneumonia | 55 (8) | 62 (0.065) | 54 (8) | 70 (0.064) | 0.9139 | 1.022 (0.677–1.543) | 1.011 (0.720–1.421) |
| Wheezing | 50 (8) | 62 (0.065) | 61 (9) | 81 (0.074) | 0.2792 | 0.806 (0.534–1.213) | 0.874 (0.629–1.215) |
| Nasopharyngitis | 44 (7) | 55 (0.057) | 48 (7) | 63 (0.058) | 0.6710 | 0.912 (0.583–1.426) | 0.997 (0.696–1.428) |
| Sinusitis | 41 (6)[b] | 52 (0.054) | 63 (9)[b] | 73 (0.067) | 0.0252 | 0.629 (0.407–0.963)[b] | 0.813 (0.571–1.159) |
| Throat irritation | 39 (6)[b] | 43 (0.045)[b] | 12 (2)[b] | 13 (0.012)[b] | 0.0001 | 3.395 (1.721–7.185)[b] | 3.777 (2.050–6.956)[b] |
| Oropharyngeal pain | 37 (6) | 43 (0.045) | 30 (4) | 32 (0.029) | 0.3768 | 1.249 (0.740–2.121) | 1.534 (0.975–2.415) |
| Nasal congestion | 26 (4) | 31 (0.032) | 37 (6) | 37 (0.034) | 0.1574 | 0.692 (0.397–1.190) | 0.957 (0.596–1.535) |
| Nasal discomfort | 23 (3) | 25 (0.026)[b] | 14 (2) | 14 (0.013)[b] | 0.1323 | 1.668 (0.814–3.539) | 2.039 (1.072–3.879)[b] |
| COPD | 20 (3) | 27 (0.028) | 13 (2) | 17 (0.016) | 0.2156 | 1.558 (0.730–3.437) | 1.813 (0.997–3.297) |
| Hemoptysis | 18 (3) | 24 (0.025)[b] | 12 (2) | 14 (0.013)[b] | 0.2661 | 1.516 (0.684–3.480) | 1.957 (1.024–3.741)[b] |
| Productive cough | 18 (3) | 19 (0.020) | 13 (2) | 14 (0.013) | 0.3613 | 1.397 (0.641–3.129) | 1.550 (0.787–3.050) |
| Respiratory failure | 12 (2) | 13 (0.014) | 11 (2) | 11 (0.010) | 0.8306 | 1.094 (0.438–2.758) | 1.349 (0.617–2.952) |
| Hypoxia | 10 (2) | 14 (0.015) | 9 (1) | 10 (0.009) | 0.8147 | 1.114 (0.404–3.122) | 1.598 (0.725–3.525) |
| Sinus congestion | 8 (1) | 9 (0.009) | 14 (2) | 15 (0.014) | 0.1983 | 0.567 (0.205–1.461) | 0.685 (0.306–1.532) |
| Asthma | 7 (1)[b] | 8 (0.008)[b] | 19 (3)[b] | 34 (0.031)[b] | 0.0177 | 0.362 (0.128–0.908)[b] | 0.269 (0.127–0.570)[b] |

Note: Listed events use preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. CI: confidence interval; COPD: chronic obstructive pulmonary disease; pt-yr: patient-years of exposure.

[a] Risk ratio calculation was based on method described by Graham et al.[8]

[b] The 95% CI on the ratio of frequencies or incidence rates excludes 1.00.

As presented in Table 3, the rate of events of bleeding from the respiratory tract was higher in the inhaled-treprostinil group (RR [95% CI]: 1.290 [1.020–1.631]). Similarly, for irritation or pain affecting the nose, mouth, larynx, or pharynx, there were both a higher rate of events and a higher proportion of patients who experienced an event in the inhaled-treprostinil group (RR [95% CI]: 2.128 [1.643–2.755]; OR [95% CI]: 1.762 [1.261–2.473]). No other notable differences between groups were observed.

## Respiratory-related AEs by baseline patient characteristics

Common respiratory-related AEs by NYHA functional class are outlined in Table 4. Among patients with more severe disease (NYHA functional class 3/4), the rate of events of cough was higher in the inhaled-treprostinil group than in the control group (RR [95% CI]: 1.599 [1.129–2.266]); however, no notable difference was detected in patients with less severe PAH (NYHA functional class 1/2). In contrast, the rate of hemoptysis events was higher in the inhaled-treprostinil group than in the control group among patients with less severe disease (RR [95% CI]: 2.554 [1.037–6.291]), but not among those with more severe disease. Regardless of disease severity, throat irritation occurred more frequently in the inhaled-treprostinil group than in the control group (class 1/2: RR [95% CI]: 4.222 [1.716–10.38], OR [95% CI]: 3.811 [1.392–12.02]; class 3/4: RR [95% CI]: 2.970 [1.318–6.690], OR [95% CI]: 2.847 [1.105–8.662]).

The most commonly reported respiratory-related AEs occurring in patients with a medical history of underlying lung disease are reported in Table 5. Cough, epistaxis, throat irritation, and COPD exacerbations demonstrated a higher number of events per patient-

Table 3. Respiratory-related adverse effects grouped by category of interest

| | Inhaled treprostinil (*N* = 666; 957.9 pt-yr) | | Control (*N* = 667; 1093.7 pt-yr) | |
|---|---|---|---|---|
| Event | Patients, no. (%)[a] | Events, no. (per pt-yr) | Patients, no. (%)[a] | Events, no. (per pt-yr) |
| Any event | 343 (52) | 867 (0.905)[b] | 338 (51) | 894 (0.817) |
| Evidence of bleeding from the upper or lower respiratory tract | 105 (16) | 148 (0.154)[b] | 93 (14) | 131 (0.120)[b] |
| Irritation or pain affecting the nose, mouth, larynx, or pharynx | 111 (17)[b] | 164 (0.171)[b] | 68 (10)[b] | 88 (0.080)[b] |
| Upper or lower respiratory tract infection | 246 (37) | 448 (0.468) | 270 (40) | 534 (0.488) |
| Wheezing, bronchospasm, or exacerbation of preexisting asthma or COPD | 79 (12) | 107 (0.112) | 89 (13) | 141 (0.129) |

Note: COPD: chronic obstructive pulmonary disease; pt-yr: patient-years of exposure.
[a] Only unique patients were included in this analysis.
[b] The 95% confidence interval on the ratio of frequencies or incidence rates excludes 1.00.

year of exposure in the inhaled-treprostinil group than in the control group (RR [95% CI]: 1.400 [1.042–1.882], 1.400 [1.021–1.920], 3.500 [1.524–8.037], and 2.250 [1.193–4.245], respectively). Only throat irritation occurred in a higher percentage of patients in the inhaled-treprostinil group than in the control group (OR [95% CI]: 3.482 [1.339–10.65]). When AEs were evaluated in a subset of patients without a medical history of underlying lung disease (Table 6), a higher number of events of cough and throat irritation were reported per patient-year among patients receiving inhaled treprostinil than among the control group (RR [95% CI]: 1.672 [1.119–2.499] and 4.053 [1.690–9.718], respectively).

Because of the observational nature of this study, PAH medications could have been adjusted throughout the study; therefore, background PAH therapies were collected at the onset of each AE. Table 7 is a summary of respiratory-related AEs by PAH therapy at onset of event in subjects receiving inhaled treprostinil. Although no statistical comparisons were made by background therapy at onset of event, the incidence of upper respiratory tract infection, epistaxis, wheezing, nasal discomfort, and nasopharyngitis increased when inhaled treprostinil was administered in combination, as compared to inhaled-treprostinil administration alone. Events of cough, bronchitis, and throat irritation remained similar between background therapies.

A between-group (inhaled treprostinil vs. inhaled iloprost [Ventavis; *n* = 41]) comparison of the most commonly reported respiratory-related AEs (occurring in ≥10% of patients in either the inhaled-treprostinil group or the inhaled-iloprost group) found no notable difference in the rate of events or proportion of patients reporting events.

One hundred sixty-eight patients (inhaled treprostinil: *n* = 95 [14%]; control: *n* = 73 [11%]) died during the study. Thirty-seven deaths (22%) were due to respiratory-related AEs (inhaled treprostinil: *n* = 18; control: *n* = 19), none of which were considered by the investigator to be attributable to inhaled-treprostinil or control therapy.

## DISCUSSION

In this study, 1,333 patients with WHO group 1 PAH receiving PAH-specific therapies were observed for respiratory-related AEs in the setting of routine clinical care. More than 950 patient-years of inhaled treprostinil exposure were included, the greatest inhaled-treprostinil exposure evaluated in a clinical study. When respiratory-related AEs were compared between treatment groups, throat irritation and cough demonstrated an increased rate of events per patient-year of exposure in the inhaled-treprostinil group relative to the control group across analyses. This respiratory-related AE profile was expected, given the route of administration and pharmacological effects of inhaled treprostinil, and was consistent with the known inhaled-treprostinil safety profile.[7,9]

Notably, the percentage of patients reporting cough in this observational study (18%) was lower than that observed in the TRIUMPH (54%) and TRIUMPH-OL studies (33%).[7,9] A decreased incidence of cough may have been observed because patients initiated inhaled-treprostinil therapy before study enrollment, with 35% of patients receiving inhaled treprostinil for more than a year at the time of study enrollment. These patients may have developed a tolerance to events of cough or optimized effective AE management strategies. Indeed, in this study, when AEs were evaluated by duration of inhaled-treprostinil exposure, a higher percentage of patients receiving inhaled treprostinil for less than 90 days reported an AE of cough (24%), as compared to those patients receiving inhaled treprostinil for more than 90 days (16%). In addition, given the relatively long duration of inhaled-treprostinil exposure before study entry, events of cough may have been captured as part of the patient medical history, with 18% of inhaled-treprostinil patients reporting a medical history of cough in this study.

Table 4. Respiratory-related adverse events reported in ≥5% of patients in either treatment group by baseline NYHA functional classification

| | Inhaled treprostinil | | Control | |
|---|---|---|---|---|
| Event, NYHA FC | Patients, no. (%) | Events, no. (per pt-yr) | Patients, no. (%) | Events, no. (per pt-yr) |
| Any event | | | | |
| 1 or 2 | 182 (63) | 573 (1.223) | 237 (59) | 768 (1.100) |
| 3 or 4 | 217 (59) | 699 (1.454) | 150 (57) | 526 (1.368) |
| Cough | | | | |
| 1 or 2 | 52 (18) | 60 (0.128) | 65 (16) | 71 (0.102) |
| 3 or 4 | 69 (19) | 94 (0.196)[a] | 40 (15) | 47 (0.122)[a] |
| Upper respiratory tract infection | | | | |
| 1 or 2 | 46 (16) | 63 (0.134) | 76 (19) | 106 (0.152) |
| 3 or 4 | 52 (14) | 65 (0.135) | 39 (15) | 52 (0.135) |
| Epistaxis | | | | |
| 1 or 2 | 40 (14) | 55 (0.117) | 41 (10) | 59 (0.084) |
| 3 or 4 | 48 (13) | 61 (0.127) | 39 (15) | 50 (0.130) |
| Nasopharyngitis | | | | |
| 1 or 2 | 23 (8) | 32 (0.068) | 37 (9) | 50 (0.072) |
| 3 or 4 | 21 (6) | 23 (0.048) | 11 (4) | 13 (0.034) |
| Pneumonia | | | | |
| 1 or 2 | 23 (8) | 25 (0.053) | 30 (8) | 36 (0.052) |
| 3 or 4 | 32 (9) | 37 (0.077) | 24 (9) | 34 (0.088) |
| Wheezing | | | | |
| 1 or 2 | 22 (8) | 28 (0.060) | 38 (10) | 52 (0.074) |
| 3 or 4 | 28 (8) | 34 (0.071) | 23 (9) | 29 (0.075) |
| Bronchitis | | | | |
| 1 or 2 | 22 (8) | 30 (0.064) | 32 (8) | 43 (0.062) |
| 3 or 4 | 34 (9) | 44 (0.092) | 24 (9) | 30 (0.078) |
| Sinusitis | | | | |
| 1 or 2 | 21 (7) | 28 (0.060) | 40 (10) | 49 (0.070) |
| 3 or 4 | 18 (5) | 22 (0.046) | 23 (9) | 24 (0.062) |
| Oropharyngeal pain | | | | |
| 1 or 2 | 18 (6) | 20 (0.043) | 19 (5) | 21 (0.030) |
| 3 or 4 | 19 (5) | 23 (0.048) | 11 (4) | 11 (0.029) |
| Dyspnea | | | | |
| 1 or 2 | 16 (5) | 17 (0.036)[a] | 37 (9) | 45 (0.064)[a] |
| 3 or 4 | 38 (10) | 45 (0.094) | 29 (11) | 40 (0.104) |
| Throat irritation | | | | |
| 1 or 2 | 16 (5)[a] | 17 (0.036)[a] | 6 (2)[a] | 6 (0.009)[a] |
| 3 or 4 | 23 (6)[a] | 26 (0.054)[a] | 6 (2)[a] | 7 (0.018)[a] |
| Nasal congestion | | | | |
| 1 or 2 | 11 (4) | 15 (0.032) | 19 (5) | 19 (0.027) |
| 3 or 4 | 15 (4) | 16 (0.033) | 18 (7) | 18 (0.047) |

Note: Listed events use preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. NYHA FC: New York Heart Association functional class; pt-yr: patient-years of exposure.

[a] The 95% confidence interval on the ratio of frequencies or incidence rates excludes 1.00.

Table 5. Respiratory-related adverse events reported in ≥5% of patients in either treatment group with a medical history of parenchymal lung disease

| | Inhaled treprostinil ($N$ = 420; 568.6 pt-yr) | | Control ($N$ = 403; 663.4 pt-yr) | |
|---|---|---|---|---|
| | Patients, no. (%) | Events, no. (per pt-yr) | Patients, no. (%) | Events, no. (per pt-yr) |
| Any event | 265 (63) | 876 (1.541)[a] | 252 (63) | 899 (1.355)[a] |
| Cough | 80 (19) | 96 (0.169)[a] | 71 (18) | 80 (0.121)[a] |
| Upper respiratory tract infection | 63 (15) | 85 (0.149) | 77 (19) | 100 (0.151) |
| Epistaxis | 63 (15) | 84 (0.148)[a] | 50 (12) | 70 (0.106)[a] |
| Pneumonia | 43 (10) | 47 (0.083) | 40 (10) | 55 (0.083) |
| Bronchitis | 40 (10) | 53 (0.093) | 40 (10) | 52 (0.078) |
| Dyspnea | 37 (9) | 43 (0.076) | 51 (13) | 68 (0.103) |
| Wheezing | 35 (8) | 46 (0.081) | 42 (10) | 58 (0.087) |
| Sinusitis | 28 (7)[a] | 35 (0.062) | 45 (11)[a] | 51 (0.077) |
| Nasopharyngitis | 27 (6) | 32 (0.056) | 30 (7) | 41 (0.062) |
| Oropharyngeal pain | 24 (6) | 28 (0.049) | 18 (4) | 20 (0.030) |
| Throat irritation | 21 (5)[a] | 21 (0.037)[a] | 6 (1)[a] | 7 (0.011)[a] |
| COPD | 20 (5) | 27 (0.047)[a] | 11 (3) | 14 (0.021)[a] |
| Nasal congestion | 17 (4) | 20 (0.035) | 26 (6) | 26 (0.039) |

Note: Listed events use preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. COPD: chronic obstructive pulmonary disease; pt-yr: patient-years of exposure.

[a] The 95% confidence interval on the ratio of frequencies or incidence rates excludes 1.00.

At enrollment, the majority of inhaled-treprostinil subjects were receiving inhaled treprostinil in combination with both an ERA and a PDE5I, as compared to inhaled treprostinil in combination with a single oral PAH therapy or as PAH monotherapy. Although the TRIUMPH study was conducted with inhaled treprostinil in combination with a single oral therapy for PAH, data from our obser-

Table 6. Respiratory-related adverse events reported in ≥5% of patients in either treatment group without a medical history of parenchymal lung disease

| | Inhaled treprostinil ($N$ = 246; 389.3 pt-yr) | | Control ($N$ = 264; 430.3 pt-yr) | |
|---|---|---|---|---|
| | Patients, no. (%) | Events, no. (per pt-yr) | Patients, no. (%) | Events, no. (per pt-yr) |
| Any event | 138 (56) | 405 (1.040) | 136 (52) | 396 (0.920) |
| Cough | 42 (17) | 59 (0.152)[a] | 35 (13) | 39 (0.091)[a] |
| Upper respiratory tract infection | 36 (15) | 44 (0.113) | 38 (14) | 58 (0.135) |
| Epistaxis | 26 (11) | 33 (0.085) | 30 (11) | 39 (0.091) |
| Dyspnea | 18 (7) | 20 (0.051) | 15 (6) | 17 (0.040) |
| Throat irritation | 18 (7)[a] | 22 (0.057)[a] | 6 (2)[a] | 6 (0.014)[a] |
| Nasopharyngitis | 17 (7) | 23 (0.059) | 18 (7) | 22 (0.051) |
| Bronchitis | 17 (7) | 22 (0.057) | 16 (6) | 21 (0.049) |
| Wheezing | 15 (6) | 16 (0.041) | 19 (7) | 23 (0.053) |
| Sinusitis | 13 (5) | 17 (0.044) | 18 (7) | 22 (0.051) |
| Oropharyngeal pain | 13 (5) | 15 (0.039) | 12 (5) | 12 (0.028) |
| Pneumonia | 12 (5) | 15 (0.039) | 14 (5) | 15 (0.035) |

Note: Listed events use preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. pt-yr: patient-years of exposure.

[a] The 95% confidence interval on the ratio of frequencies or incidence rates excludes 1.00.

Table 7. Summary of respiratory-related adverse events reported in ≥10% of inhaled-treprostinil subjects by PAH therapy reported at onset of event

| | Inhaled treprostinil alone (*N* = 38) | | Inhaled treprostinil + ERA (*N* = 54) | | Inhaled treprostinil + PDE5I (*N* = 116) | | Inhaled treprostinil + ERA + PDE5I (*N* = 213) | | Inhaled treprostinil + other background therapy (*N* = 23) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event | Patients, no. (%) | Events, no. | Patients, no. (%) | Events, no. | Patients, no. (%) | Events, no. | Patients, no. (%) | Events, no. | Patients, no. (%) | Events, no. |
| Any event | 38 (100) | 81 | 54 (100) | 160 | 116 (100) | 357 | 213 (100) | 652 | 23 (100) | 31 |
| Cough | 13 (34) | 14 | 12 (22) | 14 | 29 (25) | 35 | 70 (33) | 91 | 1 (4) | 1 |
| Bronchitis | 8 (21) | 10 | 10 (19) | 16 | 17 (15) | 22 | 23 (11) | 26 | 1 (4) | 1 |
| Upper respiratory tract infection | 5 (13) | 7 | 14 (26) | 20 | 26 (22) | 37 | 50 (23) | 61 | 4 (17) | 4 |
| Epistaxis | 5 (13) | 6 | 14 (26) | 15 | 25 (22) | 37 | 43 (20) | 57 | 2 (9) | 2 |
| Dyspnea | 4 (11) | 5 | 5 (9) | 5 | 17 (15) | 20 | 26 (12) | 28 | 5 (22) | 5 |
| Pneumonia | 4 (11) | 4 | 7 (13) | 8 | 21 (18) | 24 | 22 (10) | 24 | 2 (9) | 2 |
| Sinusitis | 4 (11) | 5 | 3 (6) | 3 | 14 (12) | 19 | 19 (9) | 23 | 1 (4) | 2 |
| Throat irritation | 4 (11) | 5 | 6 (11) | 6 | 9 (8) | 11 | 20 (9) | 21 | 0 (0) | 0 |
| Oropharyngeal pain | 3 (8) | 3 | 1 (2) | 1 | 10 (9) | 12 | 22 (10) | 24 | 2 (9) | 3 |
| Wheezing | 1 (3) | 1 | 8 (15) | 13 | 17 (15) | 20 | 22 (10) | 25 | 3 (13) | 3 |
| Nasal discomfort | 1 (3) | 1 | 6 (11) | 8 | 6 (5) | 6 | 10 (5) | 10 | 0 (0) | 0 |
| Nasopharyngitis | 1 (3) | 1 | 5 (9) | 8 | 11 (9) | 11 | 26 (12) | 34 | 1 (4) | 1 |

Note: Listed events use preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension; PDE5I: phosphodiesterase type 5 inhibitor.

vational study suggest an increased use of multiagent combination therapy, which is consistent with recent literature demonstrating improved outcomes with combination therapy.[5,7,9-13] Although only a limited number of patients were receiving inhaled treprostinil alone, when AEs were evaluated by PAH therapy at event onset, the percentage of patients reporting upper respiratory tract infection, epistaxis, wheezing, nasal discomfort, or nasopharyngitis increased when inhaled treprostinil was administered in combination, as compared to inhaled-treprostinil monotherapy. These findings must be interpreted with caution, given the small number of patients receiving inhaled treprostinil alone; however, an increased incidence of AEs is not unexpected with additional background therapy, particularly since respiratory-related AEs, including respiratory tract infections[14] and epistaxis,[15] have been reported with ERA and PDE5I therapies.

Fewer than 1% of patients in either treatment group discontinued the study because of a respiratory-related AE, suggesting that, regardless of treatment, PAH therapies are unlikely to result in respiratory-related AEs requiring the discontinuation of study therapy. This finding was consistent with the TRIUMPH study, in which 3 subjects discontinued the study drug because of respiratory-related AEs. Notably, the data from our study suggest that the respiratory-related AEs associated with inhaled treprostinil are largely transient, with symptoms resolving after therapy discontinuation.

Although only a limited number of patients were receiving inhaled iloprost ($n$ = 41) during our study, a between-group (inhaled treprostinil vs. inhaled iloprost) comparison demonstrated no notable difference in the rate of events or proportion of patients reporting events. Cough was the most commonly reported event in both treatment groups, with 18% and 20% of patients reporting cough in the Tyvaso and inhaled-iloprost groups, respectively. The results indicate that the observed respiratory-related AEs are class and route related and not unique to inhaled treprostinil.[16-19]

Although patients were required to have a clinical diagnosis of WHO group 1 PAH, the study did not exclude patients on the basis of underlying lung disease. Subsequently, a relatively large proportion of patients (62%) reported a medical history significant for parenchymal lung disease at baseline, with a similar percentage of patients reported between treatment groups (63% inhaled treprostinil vs. 60% control). Overall, a higher percentage of patients with underlying lung disease than of those without underlying lung disease reported respiratory-related AEs, which was expected, given their comorbid respiratory conditions. Notably, COPD exacerbations and epistaxis demonstrated an increased number of events in patients receiving inhaled treprostinil with a medical history significant for underlying lung disease but not in patients without a history of lung disease. This increase was likely due to the higher proportion of patients in the inhaled-treprostinil group with a medical history of COPD at baseline. Fur-

ther studies are needed to evaluate the use of inhaled treprostinil in patients with underlying lung disease.

Because of the observational design and large sample size, the results of this study are representative of patients treated with inhaled treprostinil and other PAH-specific therapies in routine clinical practice. However, because the inclusion criteria were relatively nonrestrictive and data collection was limited, there were likely confounding variables. Dosage information was not reported, so the relationship between dose and respiratory-related AEs could not be captured. Although concomitant medications, PAH-specific or otherwise, were collected, patients were not randomized to these therapies, and a causal relationship between concomitant medications and observed respiratory-related AEs could not be assessed. In the TRIUMPH study, participants were receiving a single ERA or PDE5I background therapy,[7] which differed from our study, in which the majority of patients were receiving multiple background therapies. This difference, combined with a longer study duration, may account for differences in AE rates between the studies. Prescribers must recognize the theoretical increase in risk when prescribing medications with overlapping pharmacological effects. In the case of inhaled treprostinil, concomitant anticoagulants or other medications with bleeding risk should be used with caution.[6]

*Summary*. Inhaled treprostinil was well tolerated, with fewer than 1% of patients discontinuing treatment because of a respiratory-related AE. Cough and throat irritation occurred at a higher rate in the inhaled-treprostinil group than in the control group, which was expected, given the administration route and pharmacological effects. Importantly, the overall rate of respiratory AEs did not differ between the inhaled-treprostinil and control groups. Respiratory-related AEs occurring during routine clinical use of inhaled treprostinil are consistent with its known safety profile.

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## REFERENCES

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Linder JR, Mathier MA, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association, developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53(17):1573–1619.
2. Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009;54(1 Suppl):S78–S84.
3. Zamanian RT, Kudelko KT, Sung YK, de Jesus Perez V, Liu J, Spiekerkoetter E. Current clinical management of pulmonary arterial hypertension. Circ Res 2014;115(1):131–147.
4. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007;131(6):1917–1928.
5. Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, Klepetko W, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62(25 Suppl): D60–D72.
6. Tyvaso (treprostinil) [US package insert]. Research Triangle Park, NC: United Therapeutics. 2014.
7. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 2010;55(18):1915–1922.
8. Graham PL, Mengersen K, Morton AP. Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method. Stat Med 2003;22(12):2071–2083.
9. Benza RL, Seeger W, McLaughlin VV, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubin LJ. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the treprostinil sodium inhalation used in the management of pulmonary arterial hypertension (TRIUMPH) study open-label extension. J Heart Lung Transplant 2011;30(12):1327–1333.
10. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373(9):834–844.
11. Ghofrani HA, Humbert M. The role of combination therapy in managing pulmonary arterial hypertension. Eur Respir Rev 2014;23(134):469–475.
12. Sitbon O, Jaïs X, Savale L, Cottin V, Bergot E, Macari EA, Bouvaist H, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J 2014;43(6):1691–1697.
13. Zamanian RT, Scott V, Marlin C, Gomberg-Maitland M, Preston IR, Cuttica MJ. CONFRONT PAH—an interim analysis of combination upfront therapy for pulmonary arterial hypertension clinical trial. Poster presented at the American Thoracic Society 2013 International Conference (session B64: Management of pulmonary hypertension), May 20, 2013; Philadelphia, PA.
14. Tracleer (bosentan) [US package insert]. South San Francisco, CA: Actelion Pharmaceuticals. 2015.
15. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galiè N, Simonneau G, SUPER Study Group. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol 2007; 34(12):2417–2422.
16. Hill NS, Preston IR, Roberts KE. Inhaled therapies for pulmonary hypertension. Respir Care 2015;60(6):794–805.
17. Hoeper MM, Leuchte H, Halank M, Wilkens H, Meyer FJ, Seyfarth HJ, Wensel R, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2006; 28(4):691–694.
18. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006;174(11):1257–1263.
19. Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347(5):322–329.