DOI: 10.1002/pul2.12198

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Efficacy, safety, and pharmacokinetics of inhaled treprostinil in Japanese patients with pulmonary arterial hypertension

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Funding information
Mochida Pharmaceutical Company, Grant/Award Number: N/A

Abstract

Treprostinil is a chemically stable analog of prostacyclin, and inhaled treprostinil was developed to deliver the effects directly to the pulmonary vasculature while minimizing systemic side effects. The objective of the study was to evaluate the efficacy on hemodynamics and exercise capacity, safety, and pharmacokinetics (PK) of inhaled treprostinil in Japanese patients with pulmonary arterial hypertension (PAH). Inhaled treprostinil was administered at three breaths (18 μg)/session four times daily, and the dose was gradually increased to a maximum of nine breaths (54 μg)/session. Endpoints included change in pulmonary vascular resistance index (PVRI) as primary, other efficacy parameters, safety, and PK. Seventeen PAH patients, the majority of whom (76.5%) had been receiving both an endothelin receptor antagonist (ERA) and a phosphodiesterase type-5 (PDE5) inhibitor/soluble guanylate cyclase (sGC) stimulator, received inhaled treprostinil. At Week 12, PVRI statistically decreased

by −39.4 ± 25.5% (95% confidence interval: −52.6 to −26.3). The most frequently reported adverse events related to treprostinil were headache, cough, throat irritation, and hot flush. Regarding PK, there were no notable differences in the geometric mean C_{max} and AUC_{last} between Japanese and non-Japanese patients. Treatment with inhaled treprostinil using the dosing regimen approved in the United States resulted in significant improvement in hemodynamics, exercise capacity, and symptoms with a favorable tolerability and safety profile in Japanese patients. Inhaled treprostinil could be a valuable therapeutic option for Japanese patients with PAH, including those receiving a combination therapy with an ERA and a PDE5 inhibitor/sGC stimulator. Trial registration: JAPIC Clinical Trials Information [JapicCTI-194651].

KEYWORDS
clinical trial, hemodynamics, PAH, prostacyclin, pulmonary hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive, and fatal disease, characterized by increasing pulmonary vascular resistance (PVR), which may ultimately lead to right ventricular failure and premature death.[1] Currently, PAH-specific therapy of three different drug classes is available: prostacyclin and its derivatives (belonging to the prostacyclin pathway), endothelin receptor antagonists (ERA) belonging to the endothelin pathway, phosphodiesterase type-5 (PDE5) inhibitors and soluble guanylate cyclase (sGC) stimulators belonging to the nitric oxide (NO) family.[2] In addition, initial upfront combination therapy (receiving multiple types of PAH-specific therapy from the early stage of treatment with little time lag) has become a standard treatment strategy, and appears to have an advantage in the treatment of PAH.[3]

Treprostinil is a chemically stable analog of prostacyclin, which promotes vasodilation of pulmonary and systemic arterial vascular beds, inhibits platelet aggregation and pulmonary artery smooth muscle cell proliferation and reverses pulmonary artery remodeling. Parenteral treprostinil was initially approved, and subcutaneous and intravenous administration are known to be associated with adverse effects including infusion site pain and bloodstream infections, respectively.[4,5] The TRIUMPH study, conducted in the United States and Europe, showed that inhaled treprostinil further improved exercise capacity and quality of life in PAH patients who received bosentan or sildenafil.[6] In this trial, the primary endpoint was the 6-minute walking distance (6MWD). However, efficacy of inhaled treprostinil on hemodynamic parameters was not assessed in this trial. No clinical trials of inhaled treprostinil have been conducted in Asian patients.

The objective of this study was to evaluate the efficacy on hemodynamic parameters and exercise capacity, safety, and pharmacokinetics (PK) of inhaled treprostinil in Japanese patients with PAH.

METHODS

Study design

This study was a multicenter, non-randomized, open-label, single-arm study of patients with PAH. The study consisted of a 12-week main treatment period and a 40-week long-term treatment period. Inhaled treprostinil (0.6 mg/mL) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 μg/breath. Patients initiated treprostinil inhalation at three breaths (18 μg)/session four times daily. If clinically tolerated, the dose was gradually increased to a maximum of nine breaths (54 μg)/session four times daily in three breaths increments with a minimum interval of 7 days.

Patient selection

Eligible patients were 18–75 years of age with idiopathic PAH (IPAH), heritable PAH (HPAH), drug- or toxin-induced PAH, or PAH associated with connective tissue disease or human immunodeficiency virus infection and were in World Health Organization (WHO) functional class I–IV. Patients were required to have a baseline 6MWD ≥ 200 m, and have mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg confirmed by a baseline

right heart catheterization (RHC). Patients were also required to have PVR ≥ 5 Wood units, as in recent randomized controlled trials such as the GRIPHON study.[7] Patients were able to participate in this study regardless of whether they had received previous treatment with PAH-specific therapy or not. Patients receiving an ERA and/or PDE5 inhibitor/sGC stimulator were required to have initiated >12 weeks before enrollment and had been receiving a stable dose for >4 weeks. Concomitant use of prostacyclin analog or prostacyclin receptor agonist was not permitted. The duration of enrollment was approximately 2 years.

Outcome measures

Hemodynamic measurements by RHC were performed at baseline and Week 12, both pre-inhalation, 15 min after inhalation, and 30 min after inhalation. Cardiac output (CO) was measured by the thermodilution or indirect Fick method, following the standard procedures of each institution. The same method was used for each patient both at baseline and at Week 12. Cardiac index was derived by correction of CO with body surface area (BSA): Cardiac index = CO/BSA. PVR and PVRI were calculated from trans-pulmonary pressure gradient and pulmonary blood flow: PVR = (mPAP-PAWP)/CO, and PVR index (PVRI) = (mPAP-PAWP)/Cardiac index, respectively. The primary endpoint was change in PVRI from baseline to post-inhalation of Week 12. Secondary efficacy endpoints included changes in other hemodynamic parameters, peak 6MWD, trough 6MWD, Borg Dyspnea Score, WHO functional class, N-terminal fragment of brain natriuretic peptide (NT-proBNP) levels, and quality of life (QOL) measured by the Minnesota Living with Heart Failure (MLWHF) questionnaire, and the time to clinical worsening, defined as death, transplantation, hospitalization due to worsening PAH, or initiation of additional PAH-specific therapy. Peak 6MWD was measured within 10–60 min after inhalation, and trough 6MWD was measured at least after 4 h post-inhalation.

Safety endpoints included adverse events (AEs), routine laboratory parameters measured in a clinical laboratory, vital signs (blood pressure, pulse and percutaneous arterial oxygen saturation [SpO_2]), electrocardiogram, chest X-ray, pulmonary function test, arterial blood gas analysis, and body weight.

Pharmacokinetic data

For analysis of inhaled treprostinil PK in Japanese patients, blood samples were collected at baseline and pre-inhalation, and 5, 10, 15, 30, 60, 120, and 240 min after inhalation in Week 12 for patients in this trial; and at pre-inhalation, and 5, 10, 15, 30, 60, 90, 120, 180, and 240 min after single inhalation for healthy adult volunteers. Plasma treprostinil concentrations were measured using a liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay, validated according to Guideline on Bioanalytical Method Validation in Pharmaceutical Development.[8] PK parameters, determined from the plasma concentration versus time data for treprostinil, included the maximum plasma concentration (C_{max}), plasma concentration at measurable final time point (C_{last}), time to C_{max} (T_{max}), elimination half time ($T_{1/2}$), time of the last measurable plasma concentration (T_{last}), area under the plasma concentration-time curve (AUC) from time 0 to last measurable concentration sampling time (AUC_{last}), AUC from time 0 to infinity (AUC_{inf}), percentage of AUC_{inf} based on extrapolation (AUC_{Extrap}), elimination rate constant (λ_Z), mean residence time (MRT), apparent total body clearance (CL/F) and apparent volume of distribution during the terminal phase (V_Z/F). PK data obtained from non-Japanese populations were cited from previously published literature.[9,10]

Statistical analysis

Efficacy, safety, and PK analysis sets included all patients who received one dose of treprostinil inhalation and have any one post-baseline efficacy, safety, and PK data, respectively. The lower PVRI measured at 15 or 30 min after inhalation was taken as the designated "best" PVRI at Week 12. A statistically significant difference was defined as the two-sided 95% confidence interval (CI) of the mean change from baseline to Week 12 excluding the value 0. AEs were summarized by preferred term using the Medical Dictionary for Regulatory Activities Version 24.0. All statistical analysis was performed using SAS (version 9.4).

RESULTS

Patients

A total of 17 patients (7 male and 10 female) with a mean (±SD) age of 46.4 ± 15.5 years (range 19–71 years) were enrolled at 10 centers. These included 15 patients with IPAH/HPAH and two patients with PAH associated with connective tissue disease, and the mean (±SD) time since PAH diagnoses was 4.0 ± 4.6 years (range 0.1–16.1 years). Patient demographic data are described in Table 1.

TABLE 1 Patient demographic data.

	$n = 17$
Female [n (%)]	10 (58.8)
Age (years)	
Mean ± SD	46.4 ± 15.5
PAH classification [n (%)]	
IPAH/HPAH	15 (88.2)
Associated with connective tissue disease	2 (11.8)
Time since PAH diagnosis (years)	
Mean ± SD	4.0 ± 4.6
Baseline WHO functional class [n (%)]	
II	11 (64.7)
III	6 (35.3)
Baseline 6-minute walking distance (m)	
Mean ± SD	487.8 ± 112.4
Background PAH therapy [n (%)]	
No	1 (5.9)
Yes	16 (94.1)
ERA	3 (17.6)
ERA and PDE5 inhibitor/sGC stimulator	13 (76.5)
Previous prostacyclin therapy [n (%)]	
No	8 (47.1)
Yes	9 (52.9)
Selexipag (oral)	7 (41.2)
Beraprost (oral)	2 (11.8)
Iloprost (inhalation)	1 (5.9)

Abbreviations: ERA, endothelin receptor antagonist; HPAH, heritable PAH; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type-5; sGC, soluble guanylate cyclase; WHO, World Health Organization.

WHO functional classes at baseline were class II (64.7%) and class III (35.3%). The majority of patients (76.5%) had been receiving both an ERA and a PDE5 inhibitor/sGC stimulator; only one patient was treatment-naïve. All 17 patients completed the 12-week main treatment period and 16 entered the long-term treatment period and continued to Week 52. During the 12-week period, the mean (±SD) maximum dose of treprostinil was 8.5 ± 1.1 breaths/session.

Efficacy

Hemodynamic parameters, including the primary endpoint of PVRI, at baseline and at Week 12 are summarized in Table 2. The mean (±SD) PVRI decreased from 11.6 ± 2.7 Wood units·m^2 at baseline to 6.9 ± 2.9 Wood units·m^2 at the best of Week 12. The best change from baseline in PVRI at Week 12 of −39.4 ± 25.5% (95% CI: −52.6 to −26.3) was statistically significant. The mean PVR also decreased significantly: the best change from baseline in PVR at Week 12 was −39.7 ± 25.6% (95% CI: −52.9 to −26.5). In addition, statistically significant improvement in other hemodynamic parameters at the best of Week 12 from baseline was observed: mean (±SD) mPAP decreased by −8.3 ± 6.8 mmHg (95% CI: −11.8 to −4.8); mean (±SD) CO increased by +0.8 ± 1.0 L/min (95% CI: 0.2 to 1.3); mean (±SD) cardiac index increased by +0.5 ± 0.6 L/min/m^2 (95% CI: 0.1 to 0.8). Numerical improvement in systemic vascular resistance (SVR) and SVR index (SVRI) at the best of Week 12 from baseline was also observed: mean (±SD) SVR decreased by −15.3 ± 24.0% (95% CI: −27.7 to −3.0); mean (±SD) SVRI decreased by −14.8 from −4.8% (95% CI: −27.4 to −2.3). No significant changes were observed in PAWP, mean right atrial pressure (mRAP), and mixed venous oxygen saturation (SvO_2). Importantly, PVRI, PVR, and mPAP at pre-inhalation, trough treprostinil level in Week 12 also statistically significantly decreased by −19.2 ± 26.8% (95% CI: −33.0 to −5.4), −19.6 ± 26.8% (95% CI: −33.4 to −5.8) and −4.0 ± 6.1 mmHg (95% CI: −7.1 to −0.9), respectively (Figure 1). Moreover, PVRI decreased regardless of concomitant use of PAH-specific therapy at the best of Week 12. The best change from baseline in PVRI at Week 12 was −36.7 ± 25.0% in 13 patients receiving a combination of an ERA and a PDE5 inhibitor/sGC stimulator, −46.0 ± 35.1% in three patients receiving an ERA, and −54.7% in one patient who was treatment-naïve.

The mean (±SD) changes from baseline in peak 6MWD of +19.4 ± 25.8 m (95% CI: 6.1 to 32.6) and +24.8 ± 34.2 m (95% CI: 7.2 to 42.3) at Weeks 6 and 12, respectively, were statistically significant. In addition, the mean (±SD) change from baseline in trough 6MWD at Week 12 was +17.8 ± 35.5 m (95% CI: −0.5 to 36.0). The median change from baseline in peak 6MWD at Weeks 6 and 12, and in trough 6MWD at Week 12 were +20.0 m, +34.0 m, and +23.0 m, respectively. The improvement in peak 6MWD was maintained throughout the 52 weeks (Figure 2): the mean (±SD) change from baseline of +36.3 ± 55.0 m (95% CI: 7.0 to 65.6) at Week 52 was statistically significant. No significant changes from baseline were observed in Borg Dyspnea Score at Weeks 6, 12, and 52. WHO functional class improved in four and five patients at Weeks 12 and 52, respectively; no patient experienced deterioration throughout the 52 weeks (Table 3).

The mean (±SD) changes from baseline in NT-proBNP level were −34.6 ± 100.0 pg/mL (95% CI: −86.0 to 16.8),

TABLE 2 Hemodynamic parameters ($n = 17$).

		Week 12				Change from baseline to Week 12	% Change from baseline to Week 12
			Post-inhalation			Post-inhalation	Post-inhalation
	Baseline Mean ± SD	Pre-inhalation Mean ± SD	15 min Mean ± SD	30 min Mean ± SD	Best Mean ± SD	Best Mean ± SD (95% CI)	Best Mean ± SD (95% CI)
PVRI (Wood units·m^2)	11.6 ± 2.7	9.3 ± 3.1	7.4 ± 2.8	7.3 ± 3.1	6.9 ± 2.9	−4.7 ± 3.0 (−6.2 to −3.1)	−39.4 ± 25.5 (−52.6 to −26.3)
PVR (Wood units)	7.2 ± 1.9	5.7 ± 2.2	4.5 ± 1.8	4.4 ± 2.0	4.2 ± 1.9	−2.9 ± 2.0 (−4.0 to −1.9)	−39.7 ± 25.6 (−52.9 to −26.5)
mPAP (mmHg)	38.1 ± 9.3	34.1 ± 9.8	30.5 ± 10.1	30.1 ± 10.3	29.8 ± 9.9	−8.3 ± 6.8 (−11.8 to −4.8)	−21.7 ± 19.7 (−31.9 to −11.6)
CO[a] (L/min)	4.3 ± 1.2	4.6 ± 1.3	4.9 ± 1.6	5.0 ± 1.5	5.1 ± 1.7	0.8 ± 1.0 (0.2 to 1.3)	18.3 ± 20.0 (8.0 to 28.6)
Cardiac index (L/min/m^2)	2.6 ± 0.6	2.8 ± 0.8	3.0 ± 0.9	3.0 ± 0.9	3.1 ± 0.9	0.5 ± 0.6 (0.1 to 0.8)	17.8 ± 20.3 (7.3 to 28.2)
SVR (Wood units)	20.8 ± 5.9	19.5 ± 6.2	17.8 ± 6.5	17.7 ± 6.2	17.5 ± 6.4	−3.3 ± 4.4 (−5.6 to −1.1)	−15.3 ± 24.0 (−27.7 to −3.0)
SVRI (Wood units·m^2)	33.7 ± 8.5	31.7 ± 8.7	28.8 ± 9.5	28.7 ± 9.2	28.4 ± 9.4	−5.3 ± 7.3 (−9.1 to −1.5)	−14.8 ± 24.4 (−27.4 to −2.3)
PAWP (mmHg)	7.8 ± 3.7	8.8 ± 4.1	9.4 ± 4.2	8.9 ± 3.9	8.5 ± 4.0	0.7 ± 3.9 (−1.3 to 2.7)	24.2 ± 60.9 (−7.1 to 55.5)
mRAP (mmHg)	4.8 ± 2.8	5.0 ± 3.5	4.5 ± 3.1	4.8 ± 3.3	4.4 ± 3.0	−0.4 ± 2.5 (−1.7 to 0.9)	−0.3 ± 57.0 (−31.9 to 31.2)
SvO_2 (%)	69.7 ± 4.8	71.2 ± 5.3	71.3 ± 5.6	70.0 ± 5.8	71.5 ± 5.5	1.8 ± 4.0 (−0.3 to 3.9)	2.7 ± 5.8 (−0.3 to 5.7)

Abbreviations: CO, cardiac output; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SVR, systemic vascular resistance; SvO_2, mixed venous oxygen saturation; SVRI, SVR index.

[a]CO was measured by the thermodilution ($n = 13$) or indirect Fick method ($n = 4$).

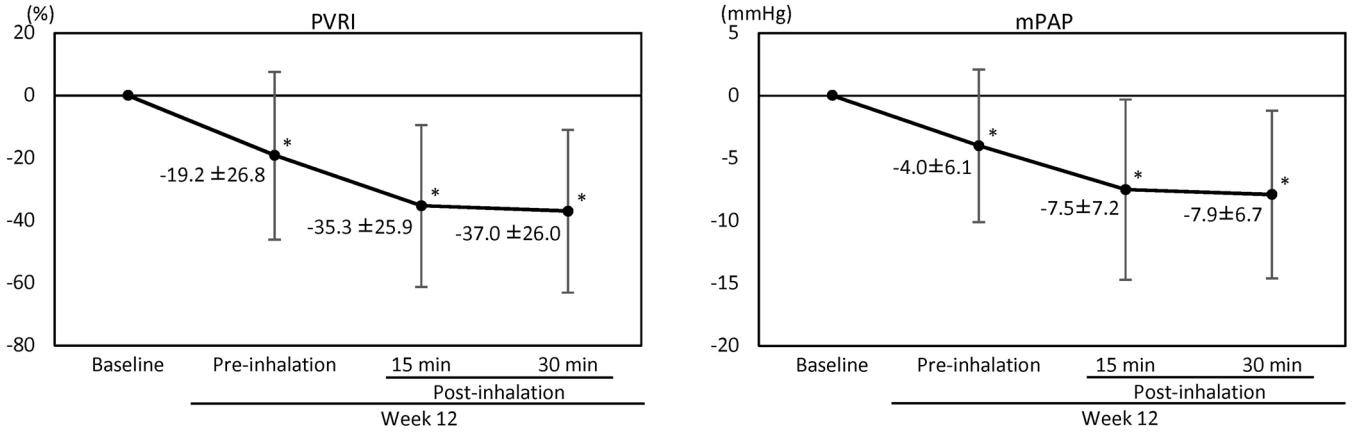

FIGURE 1 Change from baseline in hemodynamic parameters at Week 12 ($n = 17$). Data shown as the mean ± SD. mPAP, mean pulmonary arterial pressure, PVRI, pulmonary vascular resistance index. *95% CI of the mean change excludes the value 0.

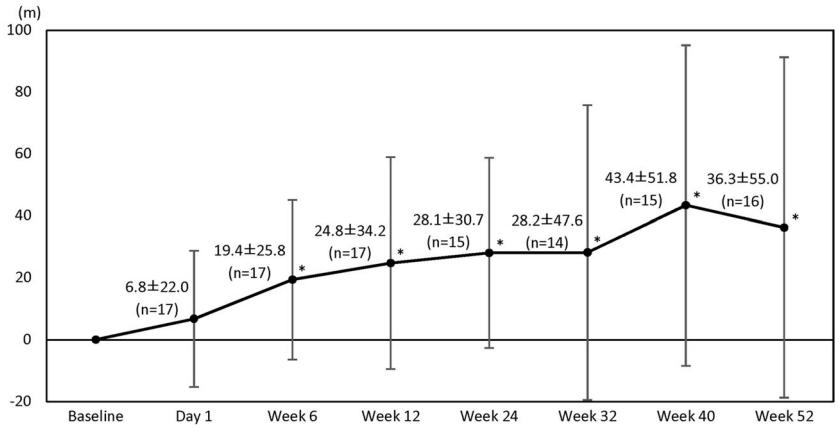

FIGURE 2 Change in peak 6-minute walking distance from baseline to Week 52. Data shown as the mean ± SD. *95% CI of the mean change excludes the value 0.

−35.5 ± 165.5 pg/mL (95% CI: −120.6 to 49.6) and −77.1 ± 194.1 pg/mL (95% CI: −180.6 to 26.3) at Weeks 6, 12 and 52, respectively. QOL as assessed by the MLWHF questionnaire had mean (±SD) changes from baseline in the global score of −6.6 ± 12.1 (95% CI: −12.8 to −0.4) and −5.8 ± 13.4 (95% CI: −13.0 to 1.3) at Weeks 12 and 52, respectively. With regard to the time to clinical worsening, no patient experienced death, transplantation, or hospitalization due to worsening PAH throughout the 52 weeks; two patients, who had been receiving an ERA, received add-on therapy with a PDE5 inhibitor/sGC stimulator in the long-term treatment period, while no patient needed additional PAH-specific therapy in the main treatment period.

Safety

Inhaled treprostinil therapy four times daily in Japanese patients with PAH was well tolerated.

AEs reported over 52 weeks are summarized in Table 4. All 17 patients reported at least one AE and AE related to treprostinil during the 52-week period. The most frequently reported AEs related to treprostinil were headache (58.8%), cough (47.1%), throat irritation (29.4%), and hot flush (23.5%). All AEs were of mild-moderate intensity. Only one patient reported serious AEs: pneumonia and pulmonary thrombosis in the long-term treatment period, and pneumonia and pulmonary thrombosis were not considered related to the study drug. Only one patient discontinued the study due to AEs: cough and throat irritation. There were no clinically relevant changes found in the laboratory parameters, vital signs, electrocardiogram, chest X-ray, pulmonary function test, arterial blood gas analysis, and body weight during the 52-week period.

Pharmacokinetics

Treprostinil was absorbed with a mean (±SD) T_{max} of 0.22 ± 0.25 h, and remained detectable in the plasma until approximately 4 h after inhalation, at the maximum dose of nine breaths (54 μg) four times daily (Figure 3). At the

TABLE 3 Summary of WHO functional class [*n* (%)].

Baseline ($n = 17$)	
II	11 (64.7)
III	6 (35.3)
Week 12 ($n = 17$)	
I	1 (5.9)
II	13 (76.5)
III	3 (17.6)
Shift from baseline to Week 12 ($n = 17$)	
II -> I	1 (5.9)
II -> II	10 (58.8)
III -> II	3 (17.6)
III -> III	3 (17.6)
Week 52 ($n = 16$)	
I	2 (12.5)
II	12 (75.0)
III	2 (12.5)
Shift from baseline to Week 52 ($n = 16$)	
II -> I	2 (12.5)
II -> II	9 (56.3)
III -> II	3 (18.8)
III -> III	2 (12.5)

Abbreviation: WHO, World Health Organization.

TABLE 4 Summary of AEs over 52 weeks ($n = 17$).

Patients with AEs [*n* (%)]	
Total patients with at least one AE	17 (100.0)
Total patients with at least one AE related to treprostinil	17 (100.0)
Deaths	0
Total patients with at least one serious AE	1 (5.9)
Total patients with at least one AE leading to withdrawal of treprostinil	1 (5.9)
AEs related to treprostinil (reported ≥ 10%)	
Headache	10 (58.8)
Cough	8 (47.1)
Throat irritation	5 (29.4)
Hot flush	4 (23.5)
Nausea	3 (17.6)
Head discomfort	3 (17.6)
Oropharyngeal discomfort	3 (17.6)
Dizziness	2 (11.8)
Oropharyngeal pain	2 (11.8)
Blood pressure decreased	2 (11.8)
Pyrexia	2 (11.8)
Diarrhoea	2 (11.8)
Palpitations	2 (11.8)

Abbreviation: AE, adverse event.

same dose, the mean (±SD) C_{max} was 1.03 ± 0.54 ng/mL; the mean (±SD) C_{last} was 0.02 ± 0.02 ng/mL; the mean (±SD) $T_{1/2}$ was 0.72 ± 0.11 h; the mean (±SD) AUC_{last} was 0.99 ± 0.57 ng·h/mL; the mean (±SD) AUC_{inf} was 1.05 ± 0.60 ng·h/mL; the mean (±SD) AUC_{Extrap} was 3.01 ± 2.16%; the mean (±SD) λ_Z was 0.98 ± 0.15/h; the mean (±SD) MRT was 0.93 ± 0.17 h; the mean (±SD) CL/F was 75.77 ± 57.58 L/h; and the mean (±SD) V_Z/F was 76.67 ± 52.24 L (Table 5).

With regard to PK in PAH patients in Japanese and non-Japanese patients, there were no notable differences in the geometric mean C_{max} (0.88 and 1.02 ng/mL, respectively) and AUC_{last} (0.84 and 0.99 ng·h/mL, respectively) at 54 μg of inhaled treprostinil, but PK parameters were somewhat lower in Japanese.[9] When PK parameters at 18 and 36 μg of inhaled treprostinil were compared in Japanese and non-Japanese healthy adults, the mean C_{max} and AUC_{inf} for Japanese adults were 1.2-fold and 1.1- to 1.3-fold higher than non-Japanese adults, respectively (Supporting Information: Table S1). When PK parameters of 54 μg of inhaled treprostinil were compared in Japanese patients with PAH, stratified by baseline characteristics, there were trends towards lower C_{max} and AUC_{last} in patients with PAH associated with connective tissue disease or those treated with no background PAH treatment or ERA alone, although the number of patients was too small to draw a conclusion (Supporting Information: Table S2).

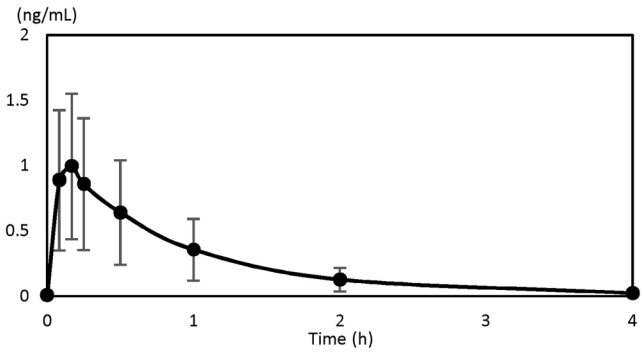

FIGURE 3 Plasma treprostinil concentration versus time following administration of 54 μg of inhaled treprostinil ($n = 12$). Data shown as the mean ± SD.

TABLE 5 Pharmacokinetic parameters of 54 μg of inhaled treprostinil.

	n	Mean ± SD
C_{max} (ng/mL)	12	1.03 ± 0.54
C_{last} (ng/mL)	12	0.02 ± 0.02
T_{max} (h)	12	0.22 ± 0.25
$T_{1/2}$ (h)	11	0.72 ± 0.11
T_{last} (h)	12	3.81 ± 0.58
AUC_{last} (ng·h/mL)	12	0.99 ± 0.57
AUC_{inf} (ng·h/mL)	11	1.05 ± 0.60
AUC_{Extrap} (%)	11	3.01 ± 2.16
λ_Z (/h)	11	0.98 ± 0.15
MRT (h)	11	0.93 ± 0.17
CL/F (L/h)	11	75.77 ± 57.58
V_Z/F (L)	11	76.67 ± 52.24

Abbreviations: AUC, area under the plasma concentration-time curve; AUC_{Extrap}, percentage of AUC_{inf} based on extrapolation; AUC_{inf}, AUC from time zero to infinity; AUC_{last}, AUC from time zero to last measurable concentration sampling time; CL/F, apparent total body clearance; C_{last}, plasma concentration at measurable final time point; C_{max}, the maximum plasma concentration; $T_{1/2}$, elimination half time; T_{last}, time of the last measurable plasma concentration; T_{max}, time to C_{max}; MRT, mean residence time; V_Z/F, apparent volume of distribution during the terminal phase; λ_Z, elimination rate constant.

DISCUSSION

This is the first study that evaluated the efficacy on hemodynamic parameters and exercise capacity, safety, and PK of inhaled treprostinil in patients with PAH in Asia. It is of note that the majority of the patients in this study were on combination therapy with an ERA and a PDE5 inhibitor/sGC stimulator. To our knowledge, this is the first clinical trial of inhaled treprostinil that demonstrates an improvement in hemodynamics over 12 weeks. As for hemodynamic parameters, the primary endpoint of change from baseline in PVRI, and the secondary endpoints of change from baseline in PVR and mPAP were significantly improved at the best of Week 12. At the fifth World Symposium on Pulmonary Hypertension, it was discussed that the primary endpoint for phase 3 clinical trials in PAH should be time to morbidity/mortality events.[11] However, such trials cannot be conducted in Japan alone, because PAH is a rare disease. Therefore, the surrogate endpoint was defined as PVRI which was reported to be a candidate predictor variable of survival in the REVEAL registry.[12] The change in PVR was also reported to be associated with adverse clinical events or mortality in treated patients with PAH in a recent meta-regression analysis of randomized controlled trials.[13] In addition, treatment with inhaled treprostinil for 12 weeks significantly decreased mPAP; lowering mPAP was recently reported to result in favorable outcomes in PAH.[14,15]

Regarding PVR and mPAP, in the IBUKI study of iloprost in Japan, the best change (lowest value among 5, 15, or 30 min after inhalation at Week 12) from baseline were −1.6 Wood units (−124 dyn·s/cm^5) and −6.75 mmHg, respectively; in the study of selexipag in Japan, the change from baseline to week 16 were −1.5 Wood units (−122.9 dyn·s/cm^5) and −3.1 mmHg, respectively.[16,17] In this study of inhaled treprostinil, greater improvements in PVR (−2.9 Wood units) and mPAP (−8.3 mmHg) were observed compared to the studies of iloprost and selexipag, although patient demographics were somewhat different between the studies (e.g., baseline WHO functional class (all patients were in WHO functional class III in the IBUKI study of iloprost) and baseline 6MWD (the mean value was approximately 90 and 70 m longer in this study than the IBUKI study of iloprost and the study of selexipag in Japan, respectively).

Importantly, PVRI, PVR, and mPAP at pre-inhalation, trough treprostinil level, of Week 12 also statistically decreased significantly, which suggests that inhaled treprostinil has not only acute vasodilation effects but also longer-term favorable effects on pulmonary arteries.

Regarding exercise capacity, in this study, peak 6MWD statistically significantly improved at Week 12 from baseline, and the improvement was maintained throughout the 52 weeks. The median change from baseline in peak 6MWD at Week 12 observed in this study and in the treatment group of the TRIUMPH study were similar (6.0% (34.0 m) and 6.9% (21.6 m), respectively). It is notable that a treatment effect of this magnitude was observed given that the majority of the patients in this study were on both an ERA and a PDE5 inhibitor/sGC stimulator. While the result in this study was numerically greater than that in the treatment group of the TRIUMPH study, results should be interpreted with caution: in the TRIUMPH study, imputation was used for missing data with worst rank for death, addition of PAH-specific therapy during the study or discontinuation due to disease progression, last rank carried forward for other missing values if a post-baseline assessment was performed, or the mean of placebo ranks if there was no post-baseline assessment; in this study, there was no missing peak 6MWD data at Week 12. 6MWD has its limitations, but it has been used as the primary endpoint in many studies including the TRIUMPH study. It is worth mentioning in this study that WHO functional class improved or was sustained,

while no patient showed deterioration throughout the 52-week period. The improvement of WHO functional class in a small group of patients might be explained by the fact that approximately two-thirds of the patients were class II at baseline.

The safety profile of inhaled treprostinil observed in this study was similar to that reported in the TRIUMPH study. The most frequently reported AEs related to treprostinil were headache, cough, throat irritation, and hot flush, which were typical of prostacyclin therapy or associated with the inhaled route of delivery of the drug. All the reported AEs related to treprostinil in this study were nonserious and of mild-to-moderate intensity. There were no deaths. Only one patient discontinued the study due to cough and throat irritation.

With regard to PK at 54 μg of inhaled treprostinil, there were no notable differences in the PK parameters in Japanese and non-Japanese patients, justifying the use of the same dosing regimen approved in the United States in Japanese patients. On the other hand, it was interesting to note that the PK parameters for Japanese patients were somewhat lower than non-Japanese patients, whereas the opposite trend was observed in healthy adults, although this was not based on direct comparison. The reason for hindering the increase in PK parameters in Japanese patients could not be identified from subgroup analyzes of this trial in Japanese patients due to the small number of patients, but it is worth investigating in future studies.

Prostacyclin therapy has long been recognized as effective for the treatment of PAH, and treprostinil is available in parenteral administration, which is associated with such potential side effects as infusion site pain or bloodstream infections. Inhaled treprostinil was developed to deliver the effects directly to the pulmonary vasculature while minimizing systemic side effects.[18] The inhaled route of delivery also avoids the risks, discomforts, and inconveniences associated with parenteral administration. Moreover, regardless of concomitant use of PAH-specific therapy, PVRI decreased at the best of Week 12. Thus, inhaled treprostinil is a valid option of the prostacyclin therapies that have clinical benefits as add-on therapy to an ERA and/or a PDE5 inhibitor/sGC stimulator in patients with PAH.

STUDY LIMITATIONS

The major limitation of this study is that it was an open-label, single-arm study design. Therefore, subjective parameters such as 6MWD and WHO functional class might be biased, compared to objective parameters such as hemodynamic parameters and NT-proBNP level. In addition, the number of patients enrolled was small and the duration of evaluation in this study was only 52 weeks. Although patients in all WHO functional classes were eligible, WHO functional class I and class IV patients were not enrolled. Finally, efficacy and safety were not compared with a placebo or active control. However, exercise capacity, symptoms, and tolerability in this study showed the same directional changes as results of the TRIUMPH study, which was a large-scale, multi-regional, randomized, double-blind, placebo-controlled study.

CONCLUSIONS

In this open-label, single-arm trial, treatment with inhaled treprostinil resulted in significant improvement in hemodynamic parameters, exercise capacity, and symptoms with a favorable tolerability and safety profile. Inhaled treprostinil could be a valuable therapeutic option for patients with PAH, including those receiving a combination therapy with an ERA and a PDE5 inhibitor/sGC stimulator.

AUTHOR CONTRIBUTIONS

Masataka Kuwana: Conceptualization; methodology; supervision; writing—review and editing. **Kohtaro Abe**, **Hideyuki Kinoshita**, **Hiromi Matsubara**, **Shun Minatsuki**, **Toyoaki Murohara**, **Seiichiro Sakao**, **Yuichiro Shirai**, **Nobuhiro Tahara**, **Ichizo Tsujino** and **Takeshi Ogo**: Investigation; writing—review and editing. **Kenta Takahashi**: Conceptualization; methodology; project administration; writing—original draft preparation; writing—review and editing. **Shingo Kanda**: Data curation; formal analysis; writing—review and editing.

ACKNOWLEDGMENTS

Statistical analysis and medical writing were supported by Mochida Pharmaceutical Co., Ltd. The authors thank all sub-investigators and clinical research coordinators. This study was funded by Mochida Pharmaceutical Co., Ltd. The sponsors of this study were involved in the study design, data collection, and analysis. Editorial assistance was supported by United Therapeutics Corporation.

CONFLICT OF INTEREST STATEMENT

MK has received grants from Boehringer Ingelheim and Ono Pharmaceutical; royalty from Medical Biological Laboratories; consulting fees from Kissei, Boehringer Ingelheim, and Mochida Pharmaceutical; lecture fees, or speaker fees from Boehringer Ingelheim, Ono Pharmaceutical., AbbVie, Asahi Kasei, Janssen Pharmaceutical,

Astellas, Chugai Pharmaceutical, Eisai, Nippon Shinyaku, Mitsubishi-Tanabe, and Mochida Pharmaceutical; participation on a data safety monitoring board or advisory board at AstraZeneka, Corbus, GlaxoSmithKline, Horizon Therapeutics, and Argenx. KA has received research funds from Mochida Pharmaceutical, Janssen Pharmaceutical, Nippon Shinyaku, Daiichi Sankyo, and Konica Minolta; speaker fees from Mochida Pharmaceutical, Janssen Pharmaceutical, Nippon Shinyaku, Bayer Yakuhin, Daiichi Sankyo, and Otsuka Pharmaceutical; fees for serving on advisory boards from Janssen Pharmaceutical. HK has received speaker fees from Nippon Shinyaku, Janssen Pharmaceutical, Bayer Yakuhin, and Mochida Pharmaceutical; consulting fees from Mochida Pharmaceutical. He belongs to the endowed department by Obama Municipal Hospital. HM has received research funds from Janssen Pharmaceutical, Nippon Shinyaku, and Mochida Pharmaceutical; lecture fees from Janssen Pharmaceutical, Bayer Yakuhin, Nippon Shinyaku, GlaxoSmithKline, and Mochida Pharmaceutical. SM has received research funds from Fukuda Foundation for Medical Technology. TM has received speaker fees from Mochida Pharmaceutical, Janssen Pharmaceutical, and Bayer Yakuhin. SS has received consulting fees from Mochida Pharmaceutical; lecture fees from Nippon Shinyaku, Bayer Yakuhin, Janssen Pharmaceuticals, Bayer AG, Pfizer, and Mochida Pharmaceutical. YS has received speaker fees from Janssen Pharmaceutical, Viatris, Nippon Shinyaku, and Mochida Pharmaceutical. NT has received lecture fees from Janssen Pharmaceutical, Nippon Shinyaku, Mochida Pharmaceutical, Pfizer, and Bayer Yakuhin. IT has received speaker fees from Mochida Pharmaceuticals. He belongs to the endowed department by Nippon Shinyaku, Boehringer Ingelheim, and Mochida Pharmaceutical. KT and SK are employees of Mochida Pharmaceutical. They have received remuneration and travel fees within the framework of their employment. TO has received lecture fees from GlaxoSmithKline, Janssen Pharmaceutical, Nippon Shinyaku, Pfizer, and Bayer Yakuhin; research grants from Pfizer, and Mochida Pharmaceutical; speaker fees from Mochida Pharmaceutical. He belongs to the endowed department of Janssen Pharmaceuticals.

GUARANTOR

Kenta Takahashi is the guarantor of the data presented in this paper.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by the local Institutional Review Boards at each site. All participants signed the informed consent form before enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kuwana M, Abe K, Kinoshita H, Matsubara H, Minatsuki S, Murohara T, Sakao S, Shirai Y, Tahara N, Tsujino I, Takahashi K, Kanda S, Ogo T. Efficacy, safety, and pharmacokinetics of inhaled treprostinil in Japanese patients with pulmonary arterial hypertension. Pulm Circ. 2023;13:e12198. https://doi.org/10.1002/pul2.12198