Inhaled treprostinil in group 3 pulmonary hypertension associated with lung disease : results of the INCREASE and PERFECT studies

Cullivan, Sarah; Genecand, Léon; El-Merhie, Natalia; MacKenzie, Alison; Lichtblau, Mona

How to cite

CULLIVAN, Sarah et al. Inhaled treprostinil in group 3 pulmonary hypertension associated with lung disease : results of the INCREASE and PERFECT studies. In: Breathe, 2025, vol. 21, n° 1, p. 240242. doi: 10.1183/20734735.0242-2024

This publication URL: https://archive-ouverte.unige.ch/unige:190459
Publication DOI: 10.1183/20734735.0242-2024

Inhaled treprostinil in group 3 pulmonary hypertension associated with lung disease: results of the INCREASE and PERFECT studies

Sarah Cullivan[1], Leon Genecand [2,3], Natalia El-Merhie [4], Alison MacKenzie[5,6] and Mona Lichtblau [7,8]

[1]National Pulmonary Hypertension Unit, Dublin, Ireland. [2]Service de pneumologie, Département de médecine, Hôpitaux universitaires de Genève, Geneva, Switzerland. [3]Faculté de médecine, université de Genève, Geneva, Switzerland. [4]Institute for Lung Health (ILH), German Center for Lung Research (DZL), Cardio-Pulmonary Institute (CPI), Universities of Giessen and Marburg Lung Center (UGMLC), Justus Liebig University, Giessen, Germany. [5]Royal Alexandra Hospital, Paisley, Glasgow, UK. [6]University of Glasgow, Glasgow, UK. [7]Clinic of pulmonology, Center for pulmonary hypertension, University Hospital Zurich, Zurich, Switzerland. [8]University of Zurich, Zurich, Switzerland.

Corresponding author: Mona Lichtblau (mona.lichtblau@usz.ch)

Shareable abstract (@ERSpublications)
While the INCREASE study in PH-ILD met its primary endpoint (change in 6MWD), the PERFECT study was stopped prematurely due to evidence that inhaled treprostinil increased serious adverse events in subjects with PH-COPD https://bit.ly/42AcrcT

Cite this article as: Cullivan S, Genecand L, El-Merhie N, *et al*. Inhaled treprostinil in group 3 pulmonary hypertension associated with lung disease: results of the INCREASE and PERFECT studies. *Breathe* 2025; 21: 240242 [DOI: 10.1183/20734735.0242-2024].

Received: 16 Oct 2024
Accepted: 27 Jan 2025

Abstract

Group 3 pulmonary hypertension (PH) associated with lung disease is a common cause of PH and is associated with substantial morbidity and mortality. Multiple studies of pulmonary arterial hypertension (PAH) therapies in this population have demonstrated conflicting results regarding their safety and efficacy, and therefore the optimum treatment for this group is unknown. The INCREASE and PERFECT randomised, double-blind, placebo-controlled trials attempted to address this unmet need by exploring the role of inhaled treprostinil (iTRE) in PH associated with interstitial lung disease (PH-ILD) and PH associated with COPD (PH-COPD), respectively. In the INCREASE and PERFECT studies individuals were randomised to placebo or iTRE, which was administered *via* an ultrasonic, pulsed-delivery nebuliser to a maximum dose of 72 µg, four times a day. The INCREASE study randomised 326 subjects with PH-ILD over a 16-week period and met its primary endpoint of change in 6-min walk distance, with a treatment effect of +31.12 m ($p<0.001$). Reduced disease progression events and increased forced vital capacity were also reported in the treatment arm in a *post hoc* analysis. By contrast, the PERFECT study was stopped prematurely by the data and safety monitoring committee due to evidence that iTRE increased serious adverse events in subjects with PH-COPD. This journal club provides an overview of these important trials and highlights pertinent unanswered questions in this field.

Commentary on:

- Waxman A, *et al*. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.
- Nathan SD, *et al*. Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results. *Eur Respir J* 2024; 63: 2400172.

Context

There have been significant advances in the treatment of group 1 pulmonary arterial hypertension (PAH) in recent decades [1]. Unfortunately, this has not been mirrored by an increase in therapeutic options for patients with group 3 pulmonary hypertension (PH) (PH associated with lung diseases). Patients with group 3 PH have worse exercise capacity, functional class and prognosis when compared to similar

patients with chronic lung disease without PH [2–6]. Severe PH associated with lung disease has recently been defined as a pulmonary vascular resistance (PVR) >5 Wood units (WU) [1].

Prospective studies of PAH therapies in group 3 PH have been limited by small sample size, inconsistent characterisation of PH and insufficient duration [7, 8]. Studies of endothelin receptor antagonists and soluble guanylate cyclase stimulators in group 3 PH have indicated a signal for harm in PH associated with interstitial lung disease (PH-ILD), raising concerns that they may worsen ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch by increasing blood flow to poorly ventilated lung [9–11]. Recent registry data has shown more promising data for phosphodiesterase type-5 inhibitors [12]. These concerns and unmet needs for disease-targeted treatments led to the conception of the INCREASE and PERFECT studies of inhaled treprostinil (iTRE) in PH-ILD and PH-COPD, respectively [13, 14].

Treprostinil is a prostacyclin analogue that was first approved for the treatment of group 1 PAH in 2002 [15]. It is a potent vasodilator of the pulmonary and systemic circulations, an inhibitor of platelet aggregation and has potential antifibrotic activity [16–19]. It can be administered *via* oral, inhaled, subcutaneous (*s.c.*) and intravenous (*i.v.*) routes, and it is typically initiated at a low dose and titrated upwards, guided by clinical symptoms and response [20, 21]. Common side-effects include diarrhoea, nausea, headache, jaw pain, flushing and dizziness. The route of administration will also influence the side-effect profile, as infusion site pain is common with *s.c.* treprostinil and cough is frequent with inhaled therapy [21].

iTRE was licensed by the US Food and Drug Administration (FDA) as the first approved therapy for PH-ILD in 2021 following the results of the INCREASE study in PH-ILD. Similar benefits were not seen with iTRE in patients with PH-COPD in the parallel PERFECT study (figure 1). This journal club provides an overview of the INCREASE and PERFECT studies, exploring the role of iTRE in PH-ILD and PH-COPD, respectively.

Methods

The INCREASE trial

The INCREASE study was a multicentre, randomised, double-blind, placebo-controlled 16-week trial of iTRE in adult subjects with PH-ILD [13]. Eligible subjects required evidence of diffuse parenchymal lung disease on computed tomography of the thorax and confirmation of PH at right heart catheterisation (RHC). A pre-capillary pattern of PH was necessary for study inclusion, comprising of a mean pulmonary artery pressure (mPAP) ⩾25 mmHg, a pulmonary artery wedge pressure (PAWP) ⩽15 mmHg, and PVR >3 WU (table 1) [13]. Subjects with group 3 PH associated with connective tissue disease (CTD) also required a baseline forced vital capacity (FVC) <70%, to avoid recruiting individuals with possible group 1 PAH.

Subjects with PH-ILD were randomised in a 1:1 fashion to placebo or drug, which was administered *via* an ultrasonic, pulsed-delivery nebuliser. The intervention group initially received iTRE at a dose of

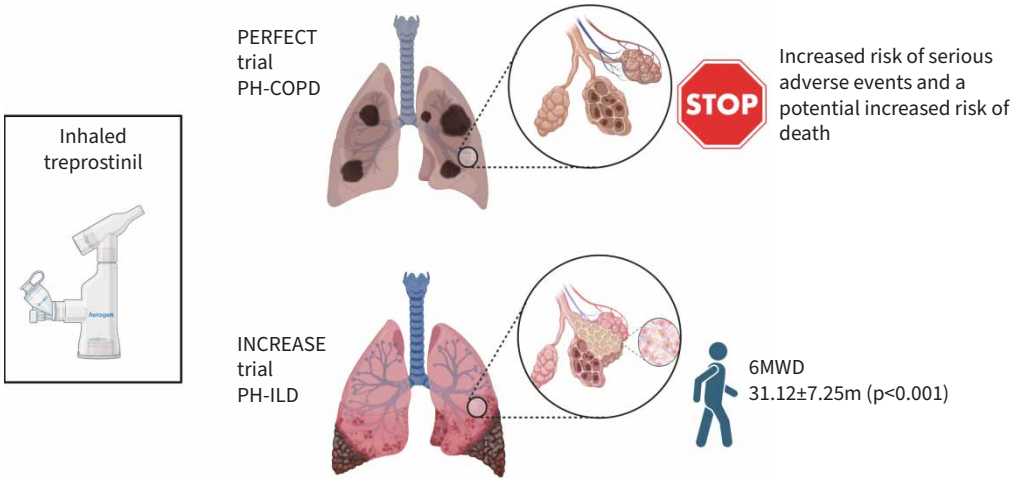

FIGURE 1 Summary of the INCREASE and PERFECT trials. PH: pulmonary hypertension; ILD: interstitial lung disease; 6MWD: 6-min walk distance. Created with BioRender.

TABLE 1 Study characteristics

	INCREASE clinical trial: iTRE in PH-ILD [13]	PERFECT clinical trial: iTRE in PH-COPD [14]
Study duration	16 weeks	12 weeks
Study design	Randomised 1:1	Randomised 1:1 Original crossover study design, with a contingent parallel design
Intervention arm	Ultrasonic, pulsed-delivery nebuliser in up to 12 breaths (total: 72 µg) four times daily	Ultrasonic, pulsed-delivery nebuliser in up to 12 breaths (total: 72 µg) four times daily
Inclusion criteria	>18 years RHC: mPAP ⩾25 mmHg, PAWP ⩽15 mmHg, PVR >3 WU Diffuse ILD confirmed on CT, including CPFE Subjects with CTD must have FVC <70% 6MWD ⩾100 m	>18 years RHC: mPAP ⩾30 mmHg, PAWP ⩽15 mmHg, PVR ⩾4 WU COPD (GOLD guidelines) FEV_1/FVC <70% pred, FEV_1 <80% pred 6MWD ⩾100 m S_{pO_2} ⩾90%
Exclusion criteria	PAH or PH group other than group 3 PH Intolerant to prostacyclin or use of PAH therapies within 60 days Significant left heart disease Supplemental oxygen >10 L·min^{-1} at rest Smoker or significant drug abuse Exacerbation of lung disease or respiratory infection within 30 days Recent initiation of pulmonary rehabilitation Acute PE within 90 days Significant comorbidity or life expectancy <6 months	Other cause for PH including group 1, 2, 4 and 5 PH Intolerant to inhaled prostanoid therapy, or use of PAH therapies at screening visit Significant left heart disease Supplemental oxygen >10 L·min^{-1} at rest Homozygous α_1-antitrypsin deficiency Exacerbation of lung disease or respiratory infection within 30 days Recent initiation of pulmonary rehabilitation (within 12 weeks) Evidence of ILD or CPFE or CHD (except for PFO) Significant comorbidity including musculoskeletal disorder that might impair study participation
Primary outcomes	Change in 6MWD	Change in 6MWD
Secondary outcomes	1) Change in NT-proBNP 2) Occurrence of clinical worsening: any event, hospitalisation for cardiopulmonary indication, decrease in 6MWD >15% from baseline, death from any cause, lung transplantation	1) Change in moderate–vigorous PA[#] 2) Change in overall PA[#] 3) Change in Borg Dyspnoea Scale 4) Change in 6MWD/Borg dyspnoea composite score 5) Change in QoL (SGRQ, SOBQ) 6) Change in NT-proBNP 7) Change in global assessment

iTRE: inhaled treprostinil; PH: pulmonary hypertension; PA: physical activity; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; WU: Wood unit; CT: computed tomography; CPFE: combined pulmonary fibrosis and emphysema; CTD: connective tissue disease; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; 6MWD: 6-min walk distance; S_{pO_2}: peripheral oxygen saturation; PE: pulmonary embolism; CHD: congenital heart disease; PFO: persistent foramen ovale; NT-proBNP: N-terminal pro-brain natriuretic peptide; QoL: quality of life; SGRQ: St George's Respiratory Questionnaire; SOBQ: University of California San Diego Shortness of Breath Questionnaire. [#]: as measured by actigraphy.

3 breaths (6 µg per breath) four times daily, which was progressively escalated to a target dose of 9 breaths four times daily. The upper limit was 12 breaths (72 µg) four times daily and drug titrations were guided by tolerance and clinical response. The control group received similar placebo inhalations. The primary endpoint was the difference in 6-min walk distance (6MWD) from baseline to week 16. Secondary outcomes are outlined in table 1 and included the change in N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to week 16 and the occurrence of clinical worsening.

The PERFECT trial

The PERFECT study was a multicentre, randomised, double-blind, placebo-controlled 12-week trial of iTRE in PH-COPD [14]. Adults with COPD (forced expiratory volume in 1 s (FEV_1)/FVC <70% predicted, FEV_1 <80% predicted) and moderate-to-severe PH confirmed at RHC (mPAP ⩾30 mmHg, PVR ⩾4 WU, PAWP ⩽15 mmHg) were included in this study (table 1). Individuals who were already receiving PH therapies or who had evidence of pulmonary fibrosis on imaging were excluded from the study. During the initial screening period subjects received low-dose iTRE to assess tolerance. The dose escalation target was 12 breaths four times daily during the study. The primary endpoint was change in 6MWD at 12 weeks, with secondary endpoints of quality of life, NTproBNP and measures of physical activity. The study had a crossover design, with a prespecified contingent parallel design, and was powered for 136 for the initial crossover design and 266 for the parallel design.

Results

The INCREASE trial

The INCREASE study enrolled 326 subjects with PH-ILD at 93 centres between 2017 and 2019. 163 subjects were randomised to each arm, with a mean age of 66.5 years (table 2). The aetiology of ILD varied and included idiopathic interstitial pneumonia in 44.8%, combined pulmonary fibrosis and emphysema (CPFE) in 25.2% and CTD-associated ILD in 22.1%. Quantification and description of emphysema in patients with CPFE is not detailed. Background antifibrotic therapy was prescribed in 22.7%.

The INCREASE study met its primary endpoint of change in peak 6MWD from baseline to week 16, demonstrating a treatment effect of +31.12 m (p<0.001). Regarding secondary endpoints, the NT-proBNP decreased by 15% with iTRE and increased by 46% from baseline with placebo, resulting in a treatment ratio of 0.58 (p<0.001). The occurrence of clinical worsening was 22.7% in the iTRE arm compared with 33.1% in the placebo arm (HR 0.61, 95% CI 0.40–0.92; p=0.04). This effect was predominantly driven by a mitigated 6MWD decline in the iTRE group when compared to placebo (8% *versus* 16%). There was no significant difference in mortality, hospitalisation and lung transplantation between iTRE and placebo.

TABLE 2 Study results

	INCREASE clinical trial: iTRE in PH-ILD [13]		PERFECT clinical trial: iTRE in PH-COPD [14]	
	iTRE (n=163)	Placebo (n=163)	Crossover (n=64)	Parallel (n=12)
Study subjects	326 randomised Intervention: 163 Control: 163		76 randomised Original crossover design: 64 Contingent parallel design: 12 Intervention: 66 Control: 58	
Female, n (%)	153 (46.9%)		33 (43%)	
Mean time since diagnosis	0.54 years		Not available	
Mean age	66.5 years		67.6 years	71.8 years
Supplemental oxygen use	71.5%		84%	83%
Mean pulmonary function tests				
FEV_1 % predicted	63.9%	65%	47%	42.6%
FVC % predicted	62.5%	63.8%	76.2%	74.8%
D_{LCO} % predicted	30%	26%	29.8%	30.4%
Mean RHC	Total (n=326)			
mPAP, mmHg	36.6		43.5	35.0
PVR, WU	6.191		7.4	6.2
PAWP, mmHg	9.8		12.35	11.0
Primary outcomes				
6MWD	Treatment effect of 31.12±7.25 m (p<0.001)		Change from baseline: −4.47 iTRE *versus* −5.14 placebo	Change from baseline: 20.33 iTRE *versus* 18.50 placebo
Secondary outcomes				
Change in NT-proBNP	Treatment effect of 0.58 (0.47–0.72), p<0.001		Full efficacy analysis was not possible due to early study termination and inadequate sample size	
Occurrence of clinical worsening[#]	Clinical worsening occurred in 22.7% in the iTRE arm *versus* 33.1% in the placebo group (HR 0.61, 95% CI 0.40–0.92; p=0.04)			
Adverse events	Cough: 43.6% (iTRE)/33% (placebo) Headache: 27.6% (iTRE)/19.6% (placebo) Dyspnoea: 25.2% (iTRE)/31.3% (placebo)		Increased serious adverse events were reported in the treatment arm, with evidence suggestive of increased mortality (6 reported deaths)	

iTRE: inhaled treprostinil; PH: pulmonary hypertension; ILD: interstitial lung disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; WU: Wood unit; PAWP: pulmonary artery wedge pressure; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide. [#]: any event, hospitalisation for cardiopulmonary indication, decrease in 6MWD >15% from baseline, death from any cause, lung transplantation.

Subgroup analyses revealed that the effect of iTRE on 6MWD was mainly observed in patients with idiopathic interstitial pneumonia and patients with CTD-ILD. No effect was observed in patients with CPFE. Similarly, no effect was observed in patients with a PVR <4 WU.

Adverse events were more common in the treatment arm when compared to placebo and included cough, headache, throat irritation and oropharyngeal pain. Withdrawal of treatment due to side-effects was common in both arms, with 47 drug discontinuations in the treatment arm and 38 in the placebo. There was no significant change in the distance–saturation product at week 16, indicating that iTRE had no dramatic effect on $\dot{V}/\dot{Q}$ matching.

Post hoc *analysis and open-label extension studies*

A *post hoc* analysis of the INCREASE study explored the efficacy of iTRE on disease progression events in subjects with PH-ILD [22]. In this study a disease progression event was defined as a >15% decline in 6MWD, an exacerbation of ILD (defined as "acute, clinically significant respiratory deterioration characterised by new widespread alveolar abnormality"), hospitalisation for cardiopulmonary disease, ⩾10% decline in FVC or death during the 16-week study period [22]. Interestingly, disease progression events were less common in the iTRE group at 147 total events when compared to 215 events in the placebo arm (p=0.018) [22]. This effect was mainly driven by a lower 6MWD decline in the treatment arm (iTRE 45 *versus* placebo 64 events) and reduced exacerbations of ILD in the iTRE arm (iTRE 48 *versus* placebo 72 events). There were no clear differences in cardiopulmonary hospitalisations (23 *versus* 33 events) and death (10 *versus* 12 events) between iTRE and placebo.

An additional *post hoc* analysis of the INCREASE study examined the effect of iTRE on FVC in PH-ILD [23]. This demonstrated improvements in the FVC in subjects receiving iTRE, with a placebo-corrected least squares mean improvement in FVC of 44.4 mL (SE 35.4; 95% CI −25.2–114.0; p=0.21) in the treatment arm. Interestingly, individuals with idiopathic pulmonary fibrosis (IPF) had the highest effect at +168.5 mL (95% CI 40.1–297 mL), paving the way for further studies exploring the role of iTRE in IPF [24].

The open-label extension (OLE) study of the INCREASE trial followed 243 subjects treated with iTRE for 108 weeks following completion of the 16-week trial [25]. This OLE supported the safety and efficacy of iTRE in PH-ILD; however, differences in 6MWD were noted when individuals were stratified by their initial treatment. Subjects who received iTRE during the initial 16-week INCREASE study experienced stabilisation of the 6MWD in the OLE. However, individuals who transitioned from placebo to iTRE during the OLE had no change in their 6MWD at week 52 [25]. The authors suggest that these results indicate that early initiation of therapy is important given the aggressive clinical course and poor prognosis of PH-ILD. However, this finding is worrisome and rarely seen in OLE studies, as typically an improvement in the primary outcome is observed when switching from placebo to the study drug. Furthermore, in the OLE study there was an extremely high discontinuation rate (172 out of 242 patients, 71%), which was primarily due to death (n=56), patient withdrawal (n=41) and adverse events (n=29). This highlights the burden of disease in the study population, the challenges of patient adherence and the considerable side-effect profile of iTRE.

In a final *post hoc* analysis, a mortality benefit of iTRE was suggested based on two modelling techniques using speculative methods to reconstruct a pseudo-placebo group from the OLE study [26]. Overall, no difference was observed in the crude mortality rate between iTRE and placebo, and these speculative assumptions should be interpreted with caution.

The PERFECT study

The PERFECT study recruited a total of 188 subjects between 2018 and 2022 across 12 sites. During the screening period, 108 subjects received ⩾1 dose of iTRE and 76 of these were subsequently randomised to the PERFECT study [14]. 64 individuals were included in the original crossover study and 12 were enrolled in the contingent parallel study that was subsequently implemented following an interim analysis by the drug and safety monitoring committee (DSMC) due to missing data and a high dropout rate. Overall 66 subjects with PH-COPD received iTRE and 58 received placebo (table 2). The clinical characteristics of the individuals enrolled in the study were consistent with severe PH, severe airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease grade 3) and severe reductions in the mean diffusing capacity of the lung for carbon monoxide (D_{LCO}) (table 2).

The study was terminated early by the DSMC as treatment with iTRE was associated with an increased risk of serious adverse events and a potential increased risk of death. The incidence of an adverse response

to iTRE was 36.4% (24 out of 66), compared with 27.6% (16 out of 58) in the placebo arm. The most common treatment-emergent serious adverse events were acute respiratory failure and COPD exacerbations. Common treatment-related adverse events included gastrointestinal disturbance, headache, cough, breathlessness and oropharyngeal pain. There were six deaths in the study, none of which were attributed to iTRE, and all subjects had a D_{LCO} ⩽25% predicted. A full efficacy analysis was not possible due to early study termination and an inadequate sample size, although it was noted that subjects receiving iTRE experienced a similar reduction in the 6MWD when compared to placebo (table 2).

The mechanism of treprostinil

Treprostinil is a prostacyclin mimetic and exerts its therapeutic effect through multiple signalling pathways. It binds to prostaglandin receptors, including the prostacyclin receptor (IP), prostaglandin E receptor 2 (EP2), and prostaglandin D receptor 1 (DP1) [27–29]. Upon activation, the IP receptor couples with adenylate cyclase, converting ATP to cyclic AMP (cAMP). This rise in cAMP activates protein kinase A (PKA), which contributes to vasodilation of pulmonary and systemic arteries by opening calcium-activated potassium channels, leading to cell hyperpolarisation while inhibiting platelet aggregation [29–33]. This cascade reduces extracellular signal-regulated kinase (Erk1/2 MAPK) signalling thereby preventing smooth muscle cell proliferation, which is crucial in attenuating pulmonary vascular remodelling [29–33]. Moreover, by activating the IP receptor, treprostinil suppresses the Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) pathway, thus inhibiting profibrotic fibroblast activity [19]. Through cAMP-mediated pathways, treprostinil also influences extracellular matrix (ECM) composition by activating CREB, which in turn prevents the excessive deposition of collagen types I and III, as well as fibronectin [16]. Various preclinical and clinical studies have shown that treprostinil inhibits lung fibroblast proliferation in a dose-dependent manner and reduces ECM deposition through cAMP-dependent and independent mechanisms in fibroblasts [16, 18, 34–37].

Treprostinil also activates peroxisome proliferator-activated receptor β (PPARβ), which enhances anti-inflammatory mechanisms, including the recruitment of the retinoid X receptor and suppression of pathways such as protein kinase C-α (PKC-α) and B cell lymphoma 6 (BCL-6) [38]. This dual action on cAMP and PPARβ signalling leads to vasorelaxation, inhibition of platelet aggregation, reduced thrombosis and attenuation of inflammation [31]. Beyond these effects, it has been demonstrated that treprostinil modulates fibrotic processes inhibiting smooth muscle cell proliferation *via* Smad6 inhibition and Smad1/5 activation, suggesting an interaction with the transforming growth factor (TGF)-β pathway [39]. It also antagonises key fibrotic drivers, such as TGF-β1 and PDGF-BB and limits collagen and fibronectin deposition *via* the NF-κB pathways [16, 18]. Treprostinil's antifibrotic effects are mediated primarily through the activation of EP2 and DP1 receptors, and play crucial roles in the inhibition of fibroblast proliferation and the reduction of collagen deposition in the lungs [34, 40]. Studies have demonstrated that even when the IP receptor is blocked, treprostinil continues to suppress cell proliferation, highlighting its dependence on EP2 activation [34]. Additionally, activation of DP1 further reduces inflammation and fibrosis by decreasing inflammatory cell recruitment and collagen accumulation in lung tissue [40]. These mechanisms address vascular and fibrotic aspects of PH-ILD, positioning treprostinil as a promising therapeutic agent for reducing fibrosis in pulmonary diseases like PH-ILD.

Commentary on the INCREASE and PERFECT studies

iTRE is a potent vasodilator, inhibitor of platelet aggregation and has potential antifibrotic properties [16–19]. The INCREASE and the PERFECT studies evaluated the safety and efficacy of iTRE in individuals with PH-ILD and PH-COPD, respectively [13, 14]. These studies differed in design and outcomes, underscoring the significant heterogeneity within group 3 PH.

The INCREASE study was a 16-week randomised controlled trial (RCT) of iTRE in PH-ILD with parallel groups, while the PERFECT study was a 12-week RCT crossover study with a washout phase and two treatment periods. The PERFECT study also had a contingent parallel design that was subsequently employed. The PERFECT study attempted to enrich for a pulmonary vascular phenotype by using higher mPAP (>30 mmHg) and PVR (>4 WU) thresholds (table 1). The primary endpoint for both studies was the change in the 6MWD from baseline.

The INCREASE study met its primary endpoint of change in 6MWD and iTRE was approved for the treatment of PH-ILD by the FDA in 2021 [13]. Approval in Europe by the European Medicines Agency is currently pending and a class IIb recommendation was provided by the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the treatment of PH-ILD [1]. Conversely, treatment of PH-COPD with iTRE in the PERFECT study was associated with increased treatment

discontinuations, serious adverse events and potential excess deaths when compared with placebo. Therefore this drug is not recommended for individuals with PH-COPD [14]. As ILD and COPD differ substantially in their epidemiology and pathophysiology, it is plausible that PH associated with these conditions requires different therapeutic approaches. ILD is typically defined by the presence of parenchymal fibrosis and inflammation, while COPD is characterised by chronic inflammation, emphysematous destruction and airway remodelling. While treprostinil can mitigate fibroblast proliferation, collagen deposition, vascular dysfunction and fibrosis, these benefits may be less pronounced in PH-COPD as fibrosis is not a central feature of the disease. The potential role of iTRE as an antifibrotic therapy for ILD will be explored in the TETON programme (TETON 1 and 2) [24]. These are comprised of two replicate randomised, double-blind placebo-controlled studies that will examine the role of iTRE in IPF over a 52-week period (clinicaltrials.gov identifiers: NCT04708782, NCT05255991) [24].

The results of the PERFECT study clearly demonstrates that the risks of iTRE in PH-COPD outweigh the potential benefits [14]. There may be a subgroup with PH-COPD with a pulmonary vascular phenotype, who might still benefit from PH therapies and the results of the PERFECT study should be used to inform future study design [41]. In the PERFECT study subjects with a treatment response had a mPAP $\geqslant$40 mmHg and FEV_1 $\geqslant$40% predicted, while those who died had a D_{LCO} $\leqslant$25%; however, the degree of emphysema among study participants was not quantified. This study underscores the importance of managing these patients in expert centres and that any decisions regarding treatment with PAH therapies should be made by a multidisciplinary team. There is a considerable unmet need in PH-COPD and additional research is necessary to clarify how best to treat these patients. It is important to be cognisant that COPD is a common comorbidity and may be present in patients with other causes for PH that are amenable to specific therapies and interventions, including PAH and chronic thromboembolic PH. These patients should continue to be treated as per the 2022 ESC/ERS PH guidelines [1].

The efficacy of iTRE for individuals with overlapping features of ILD and COPD, such as those with CPFE, remains unclear. In the INCREASE study, CPFE accounted for 25.2% of the total study population, while patients with CPFE were excluded from the PERFECT study. In the INCREASE trial, subgroup analysis revealed no effect on 6MWD in patients with CPFE. It is plausible that comorbid emphysema may have a negative impact on the efficacy and safety of PAH therapies in patients with PH-ILD [9]. Therefore, CPFE represents a unique therapeutic challenge where it seems logical to advocate for individualised treatment, as the benefit of iTRE remains uncertain and may depend on the relative extent of underlying emphysema *versus* fibrosis.

These studies were limited by their short duration and the use of the 6MWD as a primary outcome. The reliance on the 6MWD as a primary measure has progressively diminished in recent years, as it has failed to consistently demonstrate significant associations with short- and long-term outcomes, including the need for hospitalisation, lung transplantation or death [42]. In addition, the difference in the 6MWD observed in the INCREASE trial was very close to the minimal clinically important differences (ranging between 21.7 and 37 m). Furthermore, the PERFECT study was fundamentally limited by an insufficient sample size, due to early termination of the study. It was conducted solely in North America and recruitment and retention were poor. Also, the median D_{LCO} in the initial treatment arm of the PERFECT study was severely impaired at 25%, which is associated with increased mortality and a mitigated response to PAH-specific therapies [43].

Conclusion

Group 3 PH associated with lung disease is common and includes patients with PH-ILD and PH-COPD. iTRE was the first approved therapy for patients with PH-ILD and is currently under investigation as a potential antifibrotic therapy for subjects with IPF. However, iTRE should be avoided in individuals with PH-COPD as it is associated with a considerable side-effect profile, an increased risk of serious adverse events and potentially excess mortality. Future studies in group 3 PH should attempt to identify characteristics of patients with PH-COPD who respond favourably to PAH therapies. At present PAH therapies should not be broadly prescribed for individuals with PH-COPD and any decisions regarding these agents should be made in an expert PH centre.

Conflict of interest: S. Cullivan has no conflicts of interest in relation to this article. L. Genecand reports travel and speaker grants from MSD and Johnson & Johnson, outside of the submitted work. N. El-Merhie has no conflicts of interest in relation to this article. A. MacKenzie has no conflicts of interest in relation to this article. M. Lichtblau reports travel and speaker grants from MSD, Johnson & Johnson and Orpha Swiss, outside the submitted work.

References

1 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.
2 Dhont S, Zwaenepoel B, Vandecasteele E, *et al.* Pulmonary hypertension in interstitial lung disease: an area of unmet clinical need. *ERJ Open Res* 2022; 8: 00272-2022.
3 Nathan SD, Barbera JA, Gaine SP, *et al.* Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019; 53: 1801914.
4 Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. *Clin Chest Med* 2013; 34: 695–705.
5 Hurdman J, Condliffe R, Elliot CA, *et al.* Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J* 2013; 41: 1292–1301.
6 Vizza CD, Hoeper MM, Huscher D, *et al.* Pulmonary hypertension in patients with COPD: results from the comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA). *Chest* 2021; 160: 678–689.
7 Bajwa AA, Shujaat A, Patel M, *et al.* The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease. *Pulm Circ* 2017; 7: 82–88.
8 Faria-Urbina M, Oliveira RKF, Agarwal M, *et al.* Inhaled treprostinil in pulmonary hypertension associated with lung disease. *Lung* 2018; 196: 139–146.
9 Nathan SD, Behr J, Collard HR, *et al.* Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *Lancet Respir Med* 2019; 7: 780–790.
10 Zisman DA, Schwarz M, Anstrom KJ, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.
11 Blanco I, Santos S, Gea J, *et al.* Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. *Eur Respir J* 2013; 42: 982–992.
12 Tello K, Yogeswaran A, Majeed RW, *et al.* Association of phosphodiesterase-5 inhibitor treatment with improved survival in pulmonary hypertension associated with COPD in the Pulmonary Vascular Research Institute GoDeep meta-registry. *Chest* 2025; 167: 224–240.
13 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.
14 Nathan SD, Argula R, Trivieri MG, *et al.* Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results. *Eur Respir J* 2024; 63: 2400172.
15 Simonneau G, Barst RJ, Galie N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165: 800–804.
16 Lambers C, Roth M, Jaksch P, *et al.* Treprostinil inhibits proliferation and extracellular matrix deposition by fibroblasts through cAMP activation. *Sci Rep* 2018; 8: 1087.
17 Roberts MJ, May LT, Keen AC, *et al.* Inhibition of the proliferation of human lung fibroblasts by prostacyclin receptor agonists is linked to a sustained cAMP signal in the nucleus. *Front Pharmacol* 2021; 12: 669227.
18 Nikitopoulou I, Manitsopoulos N, Kotanidou A, *et al.* Orotracheal treprostinil administration attenuates bleomycin-induced lung injury, vascular remodeling, and fibrosis in mice. *Pulm Circ* 2019; 9: 2045894019881954.
19 Zmajkovicova K, Menyhart K, Bauer Y, *et al.* The antifibrotic activity of prostacyclin receptor agonism is mediated through inhibition of YAP/TAZ. *Am J Respir Cell Mol Biol* 2019; 60: 578–591.
20 Lang IM, Gaine SP. Recent advances in targeting the prostacyclin pathway in pulmonary arterial hypertension. *Eur Respir Rev* 2015; 24: 630–641.
21 McLaughlin VV, Benza RL, Rubin LJ, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010; 55: 1915–1922.
22 Nathan SD, Tapson VF, Elwing J, *et al.* Efficacy of inhaled treprostinil on multiple disease progression events in patients with pulmonary hypertension due to parenchymal lung disease in the INCREASE trial. *Am J Respir Crit Care Med* 2022; 205: 198–207.
23 Nathan SD, Waxman A, Rajagopal S, *et al.* Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a *post-hoc* analysis of the INCREASE study. *Lancet Respir Med* 2021; 9: 1266–1274.
24 Nathan SD, Behr J, Cottin V, *et al.* Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis. *BMJ Open Respir Res* 2022; 9: e001310.
25 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study. *Eur Respir J* 2023; 61: 2202414.
26 Nathan SD, Johri S, Joly JM, *et al.* Survival analysis from the INCREASE study in PH-ILD: evaluating the impact of treatment crossover on overall mortality. *Thorax* 2024; 79: 301–306.
27 Kolb M, Orfanos SE, Lambers C, *et al.* The antifibrotic effects of inhaled treprostinil: an emerging option for ILD. *Adv Ther* 2022; 39: 3881–3895.

28 Aronoff DM, Peres CM, Serezani CH, *et al.* Synthetic prostacyclin analogs differentially regulate macrophage function *via* distinct analog-receptor binding specificities. *J Immunol* 2007; 178: 1628–1634.

29 Lindegaard Pedersen M, Krüger M, Grimm D, *et al.* The prostacyclin analogue treprostinil in the treatment of pulmonary arterial hypertension. *Basic Clin Pharmacol Toxicol* 2020; 126: 32–42.

30 Schubert R, Serebryakov VN, Engel H, *et al.* Iloprost activates KCa channels of vascular smooth muscle cells: role of cAMP-dependent protein kinase. *Am J Physiol* 1996; 271: C1203–C1211.

31 Mitchell JA, Ahmetaj-Shala B, Kirkby NS, *et al.* Role of prostacyclin in pulmonary hypertension. *Glob Cardiol Sci Pract* 2014; 2014: 382–393.

32 Clapp LH, Turcato S, Hall S, *et al.* Evidence that Ca^{2+}-activated K^{+} channels play a major role in mediating the vascular effects of iloprost and cicaprost. *Eur J Pharmacol* 1998; 356: 215–224.

33 Whittle BJ, Silverstein AM, Mottola DM, *et al.* Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. *Biochem Pharmacol* 2012; 84: 68–75.

34 Patel JA, Shen L, Hall SM, *et al.* Prostanoid EP receptors are up-regulated in human pulmonary arterial hypertension: a key anti-proliferative target for treprostinil in smooth muscle cells. *Int J Mol Sci* 2018; 19: 2372.

35 Roberts MJ, Broome RE, Kent TC, *et al.* The inhibition of human lung fibroblast proliferation and differentiation by Gs-coupled receptors is not predicted by the magnitude of cAMP response. *Respir Res* 2018; 19: 56.

36 Blumer S, Fang L, Chen WC, *et al.* IPF-fibroblast Erk1/2 activity is independent from microRNA cluster 17–92 but can be inhibited by treprostinil through DUSP1. *Cells* 2021; 10: 2836.

37 Corboz MR, Zhang J, LaSala D, *et al.* Therapeutic administration of inhaled INS1009, a treprostinil prodrug formulation, inhibits bleomycin-induced pulmonary fibrosis in rats. *Pulm Pharmacol Ther* 2018; 49: 95–103.

38 Ding M, Tolbert E, Birkenbach M, *et al.* Treprostinil, a prostacyclin analog, ameliorates renal ischemia-reperfusion injury: preclinical studies in a rat model of acute kidney injury. *Nephrol Dial Transplant* 2021; 36: 257–266.

39 Yang J, Li X, Al-Lamki RS, *et al.* Smad-dependent and Smad-independent induction of Id1 by prostacyclin analogues inhibits proliferation of pulmonary artery smooth muscle cells *in vitro* and *in vivo*. *Circ Res* 2010; 107: 252–262.

40 van den Brule S, Wallemme L, Uwambayinema F, *et al.* The D prostanoid receptor agonist BW245C [(4S)-(3-[(3R,S)-3-cyclohexyl-3-hydroxypropyl]-2,5-dioxo)-4-imidazolidineheptanoic acid] inhibits fibroblast proliferation and bleomycin-induced lung fibrosis in mice. *J Pharmacol Exp Ther* 2010; 335: 472–479.

41 *ERJ* Podcast June 2024: Inhaled treprostinil in pulmonary hypertension associated with COPD. *Eur Respir J* 2024; 63: 24E6306.

42 Harari S, Wells AU, Wuyts WA, *et al.* The 6-min walk test as a primary end-point in interstitial lung disease. *Eur Respir Rev* 2022; 31: 220087.

43 van der Bruggen CE, Spruijt OA, Nossent EJ, *et al.* Treatment response in patients with idiopathic pulmonary arterial hypertension and a severely reduced diffusion capacity. *Pulm Circ* 2017; 7: 137–144.