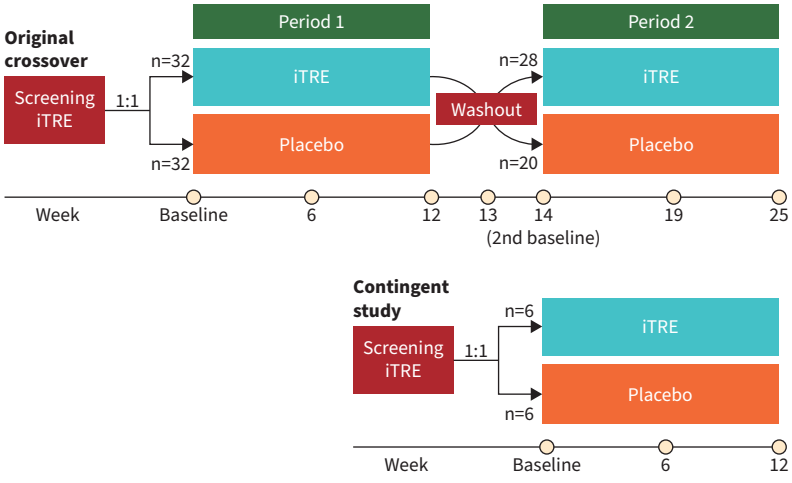
Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results

Steven D. Nathan, Rahul Argula, Maria G. Trivieri, Sameh Aziz, Elizabeth Gay, Boris Medarov, Joseph Parambil, Amresh Raina, Michael G. Risbano, Thenappan Thenappan, Jose Soto Soto, Heidi Bell, Victoria Lacasse, Prakash Sista, Michael Di Marino, Aimee Smart, Brittanie Hawkes, Elizabeth Nelson, Todd Bull, Victor Tapson and Aaron Waxman

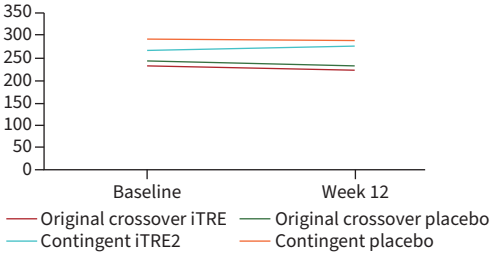
Treatment with inhaled treprostinil (iTRE) in patients with moderate to severe pulmonary hypertension (PH) due to COPD

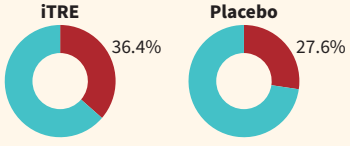
A contingent study was implemented based on missing data



Patients on iTRE showed no improvement in 6MWD comparable to placebo

Distance walked (m)	Original crossover		Contingent parallel	
	iTRE (n=60)	Placebo (n=52)	iTRE (n=6)	Placebo (n=6)
Baseline				
Median	234.00	242.50	268.00	293.00
Week 12				
Median	224.00	233.50	276.00	289.50
Change from baseline				
Median	0.00	0.00	8.00	24.50





Safety and conclusion: More patients on iTRE had an adverse response to treatment
The risk-benefit observations associated with iTRE in patients with PH-COPD did not support continuation of the PERFECT study

The results of this study do not support iTRE as a viable treatment option in patients with PH-COPD

GRAPHICAL ABSTRACT Overview of the PERFECT study.

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Shareable abstract (@ERSpublications)
Use of inhaled treprostinil in patients with pulmonary hypertension associated with COPD did not demonstrate a positive risk–benefit ratio in favour of treatment https://bit.ly/3JALxHf

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Abstract

Background Pulmonary hypertension (PH) accompanying COPD (PH-COPD) is associated with worse outcomes than COPD alone. There are currently no approved therapies to treat PH-COPD. The PERFECT study (ClinicalTrials.gov: NCT03496623) evaluated the safety and efficacy of inhaled treprostinil (iTRE) in this patient population.

Methods Patients with PH-COPD (mean pulmonary arterial pressure ⩾30 mmHg and pulmonary vascular resistance ⩾4 WU) were enrolled in a multicentre, randomised (1:1), double-blind, placebo-controlled, 12-week, crossover study. A contingent parallel design was also prespecified and implemented, based on a blinded interim analysis of missing data. Patients received treatment with iTRE up to 12 breaths (72 µg) 4 times daily or placebo. The primary efficacy end-point was change in peak 6-min walk distance (6MWD) at week 12.

Results In total, 76 patients were randomised, 64 in the original crossover design and 12 in the contingent parallel design; 66 patients received iTRE and 58 received placebo. The study was terminated early at the recommendation of the data and safety monitoring committee based on the totality of evidence that iTRE increased the risk of serious adverse events and suggestive evidence of an increased risk of mortality. The change in 6MWD was numerically worse with iTRE exposure than with placebo exposure.

Conclusions The risk–benefit observations associated with iTRE in patients with PH-COPD did not support continuation of the PERFECT study. The results of this study do not support iTRE as a viable treatment option in patients with PH-COPD.

Introduction

Pulmonary hypertension (PH) frequently complicates the course of patients with COPD. The estimated prevalence spans a wide spectrum with a reported range from 1% to over 80% [1, 2]. When PH does supervene in COPD patients, it is associated with worsened functional status and reduced survival [1, 3]. There have been numerous studies evaluating various pulmonary arterial hypertension (PAH) therapies in COPD patients, but most of these have been small, open-label or retrospective. Nonetheless, two meta-analyses of these trials have suggested a treatment benefit [4, 5]. There have been very few

randomised controlled studies for PH-COPD; one small study of sildenafil was positive, but a larger study of tadalafil was negative [6–8].

Inhaled treprostinil (iTRE) is a prostacyclin analogue indicated and approved in the USA for the treatment of Group 1 (PAH) and Group 3 (PH associated with interstitial lung disease (PH-ILD)) [9]. The latter indication was based on the results of the INCREASE study [10, 11], which remains the largest randomised controlled trial in Group 3 PH to date. The 16-week study met its primary end-point of placebo-corrected change in 6-min walk distance (6MWD) as well as numerous secondary end-points, including time to clinical worsening and change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), with a good safety profile in patients with PH-ILD.

Separately, a parallel trial to evaluate the use of iTRE in PH-COPD was initiated (PERFECT; ClinicalTrials.gov: NCT03496623). This study was a double-blind, randomised controlled trial of patients with COPD who had PH as documented by right heart catheterisation. The study was terminated early at the behest of the data and safety monitoring committee (DSMC) on 20 September 2022 due to an absence of a risk–reward benefit. Herein we report the results of the PERFECT study.

Methods

The PERFECT study was a multicentre, randomised, double-blind, placebo-controlled trial. The study included an original crossover design with two Treatment Periods and, per US Food and Drug Administration advice, a contingent design based on the potential for uninterpretable data due to a high rate of discontinuations in Treatment Period 2 (figures 1 and 2).

The original crossover study started with a screening period, during which all prospective patients received low-dose iTRE (3 breaths (0.6 mg·mL^{-1}, 6 µg per breath) 4 times a day) for 14–18 days to ensure tolerability and compliance. Any patients who were intolerant of iTRE, unable to follow the dosing

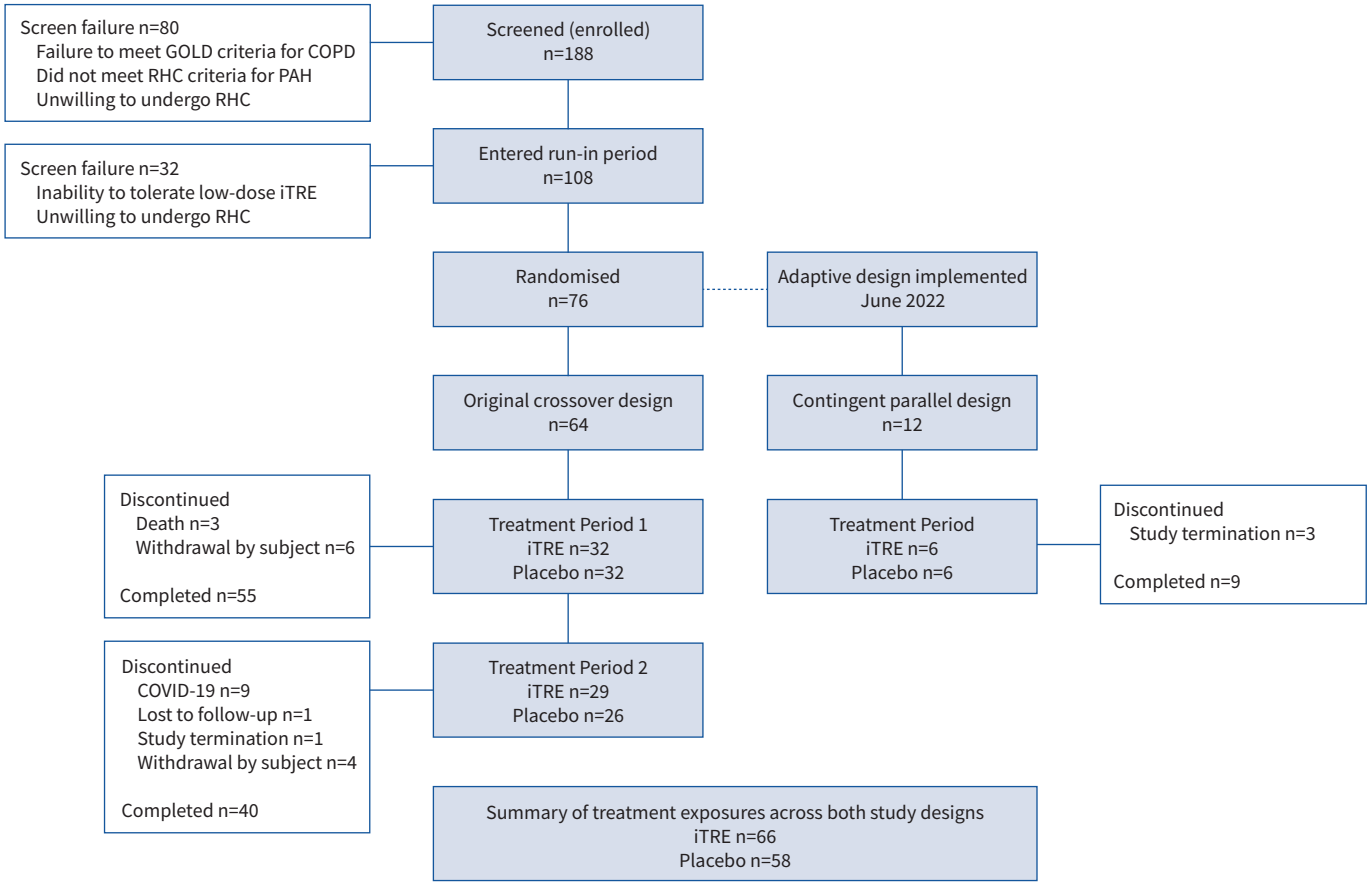

FIGURE 1 Subject disposition. GOLD: Global Initiative for Chronic Obstructive Lung Disease; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; COVID-19: coronavirus disease 2019; iTRE: inhaled treprostinil.

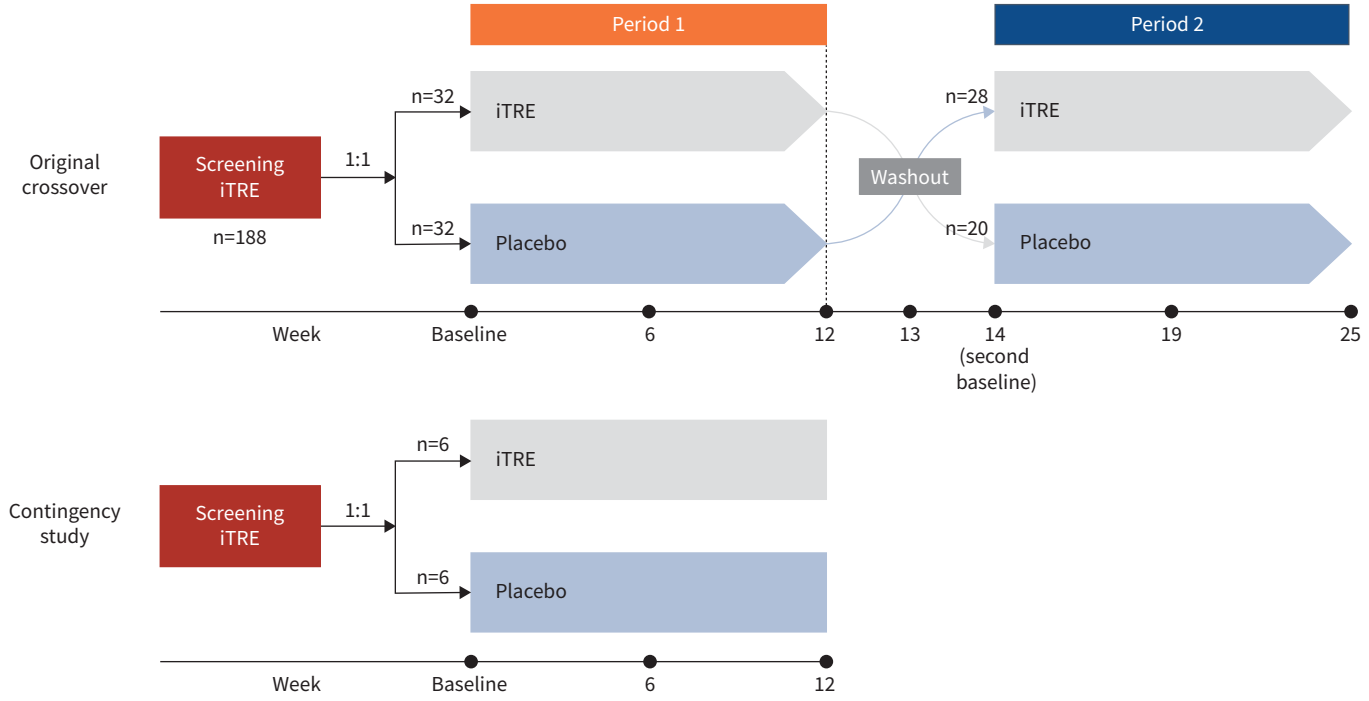

FIGURE 2 Study design for crossover or contingency scenario. iTRE: inhaled treprostinil.

regimen or non-compliant (as determined by the site principal investigator) were ineligible for randomisation. Remaining patients were then randomised 1:1 to iTRE or placebo for 12 weeks followed by a 1-week washout period before crossing over to the other arm for an additional 12 weeks of treatment.

The contingent study design was comprised of parallel cohorts of active and placebo arms without a crossover. Patients underwent 14 weeks of treatment over a 21-week period, with a single washout period (7 days minimum, 14 days maximum) and 12 weeks on active drug or placebo, per randomisation, during a single treatment period. For this contingent design, three treatment visits to the clinic were required at baseline, week 6 and week 12.

Study drug doses were titrated based on tolerability with dose escalations (additional 1 breath 4 times a day) occurring approximately every 3 days with a target dose of 12 breaths 4 times a day or the maximum tolerated dose. Dose adjustments were made based on subject tolerability at the discretion of the principal investigator at each site.

Patients who remained on study drug and completed all treatment period assessments (week 25 in the original crossover design or week 12 in the contingent parallel design) were provided the option of enrolling in an open-label extension (OLE) study.

The steering committee, in collaboration with the study sponsor, was responsible for the design and implementation of the study. The study protocol was approved by the institutional review board at the respective participating sites and was monitored by an independent DSMC. The study was conducted in accordance with the principles of Good Clinical Practice. All participants provided written informed consent prior to enrolment in the study. A list of trial personnel including the investigators and trial committees is provided in supplementary material S1. Analysis of the data was performed by the sponsor in accordance with a prespecified statistical analysis plan. The manuscript was written by the steering committee, principal investigators and authors affiliated with the sponsor, and was reviewed and approved by all authors. The authors assume responsibility for the accuracy and completeness of the data and analyses.

Trial population

The study population consisted of patients aged ⩾18 years with a diagnosis of COPD as per the 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria and a documented forced expiratory volume in 1 s (FEV_1) <80% predicted with a FEV_1/forced vital capacity (FVC) ratio

<70% during screening [12]. Patients had confirmation of moderate to severe PH based on right heart catheterisation within 1 year prior to randomisation, with a mean pulmonary arterial pressure (mPAP) ⩾30 mmHg, pulmonary vascular resistance (PVR) ⩾4 WU and pulmonary capillary wedge pressure ⩽15 mmHg. Additionally, patients were required to have a resting saturation peripheral capillary oxygenation ⩾90% during screening (with or without supplemental oxygen), and supplemental oxygen could not exceed 10 $L \cdot min^{-1}$. Eligible patients also had to have a 6MWD of ⩾100 m.

Exclusion criteria included any other cause for PH, including evidence of Group 1, 2, 4 or 5 PH as well as any evidence of ILD or combined pulmonary fibrosis and emphysema. Patients could not be on any approved therapy for PAH. The full inclusion and exclusionary criteria are included in supplementary material S2.

Main outcome measures

The primary end-point of the study was the placebo-corrected change from baseline in 6MWD following 12 weeks of active treatment. Secondary end-points included change in moderate to vigorous physical activity as measured by actigraphy, change in overall activity as measured by actigraphy, change in Borg dyspnoea score from baseline, change in 6MWD/Borg dyspnoea composite score from baseline, change in quality of life (QoL) from baseline as measured by the St George's Respiratory Questionnaire and the University of California San Diego Shortness of Breath Questionnaire, change in plasma concentration of NT-proBNP from baseline, and change in patient global assessment.

Safety end-points included all adverse events (AEs), laboratory assessments, ECGs, oxygenation, pulmonary function tests, vital sign measurements and at-home spirometry. Exploratory end-points are included in supplementary material S4.

6MWD, NT-proBNP, spirometry, QoL and standard safety measures were obtained at baseline and at study weeks 1, 6 and 12 for each period. A full list of key study activities is included in supplementary material S3.

Patients were contacted at least weekly during study drug titration and washout period(s) to assess study drug tolerance, AEs and changes in concomitant medications. As the study was conducted during the severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 (COVID-19)) pandemic, patients could have telemedicine visits in lieu of onsite visits if an onsite study visit posed a safety risk. An early termination visit was conducted for patients who discontinued prior to their final study visit.

Post hoc *analysis*

The sponsor and steering committee undertook a number of *post hoc* analyses to identify adverse responders and possibly potential responders to provide guidance into inclusionary/exclusionary criteria for future clinical trials of PH-COPD treatments. Adverse responders were defined as patients who had a decrease of ⩾15% in 6MWD at either 6 or 12 weeks of treatment, or who died or withdrew consent from the study before completing 12 weeks of treatment. Potential responders were defined as patients with a 15% increase in 6MWD accompanied by a 20% decrease in NT-proBNP [13] at either 6 or 12 weeks.

Statistical analysis

A total of 136 patients were planned for the original crossover design to ensure at least 124 evaluable patients completed the study. For the contingent parallel design, a total of 314 patients were planned to ensure at least 266 evaluable patients completed the study.

Statistical analyses were not conducted on efficacy parameters due to the early study termination and lack of appropriate sample size. Descriptive statistics are presented for the primary end-point measurement of 6MWD. The safety population was defined as all screened (enrolled) patients who received ⩾1 doses of low-dose iTRE or placebo. For the safety analyses, AEs, clinical laboratory assessments, 12-lead ECGs, oxygenation, pulmonary function tests and vital signs were summarised by treatment and by visit, when applicable. No formal inferential testing was conducted for the safety analyses. Statistical analyses were performed using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) or other validated software.

Results

During the screening period, 188 patients were screened and 108 received ⩾1 doses of iTRE (figure 1). In total, 76 patients were randomised (64 patients in the original crossover design and 12 in the contingent parallel design). Of the randomised patients, 66 patients received iTRE and 58 received placebo. For the 64 patients randomised under the original crossover design, 32 (50%) patients received iTRE and 32 (50%) received placebo in the first period of the study. For the patients that remained for Treatment Period 2

(crossover period), 28/29 (96.6%) received iTRE and 20/26 (76.9%) received placebo. Of the 12 patients randomised under the contingent parallel design, six (50%) received iTRE and six (50%) received placebo. See table 1 for detailed baseline characteristics.

A prespecified blinded interim analysis for missing data revealed that ⩾15% of the primary end-point data at week 25 were missing, which triggered the switch from the crossover design to the contingent parallel design. The study was terminated at the recommendation of the DSMC due to an overall lack of favourable benefit compared to risk profile in the study.

A total of 41 patients elected to continue in the OLE (53.9% of the total randomised population and 83.7% of those who completed the study). The results of patient outcomes for those participating in the OLE study will be communicated separately.

The intended maintenance dose for patients was 12 breaths (72 µg), and 39% of iTRE and 62% of placebo patients achieved this target. The median treatment duration during the study was 82.5 days for those who received iTRE and 84.0 days for placebo.

Over the course of the study, 27 (35.5%) patients discontinued treatment or were prematurely terminated during the study due to COVID-19 (n=9), withdrawn consent (n=10) of which two died during follow-up, early study termination by the sponsor (n=4) or death (n=3) and one subject was lost to follow-up (figure 1).

Efficacy

At week 12, patients who received iTRE experienced a decline in 6MWD comparable to placebo (table 2). Full efficacy analyses were not completed due to the study termination and lack of appropriate sample size.

Safety

Patients treated with iTRE experienced higher rates of AEs compared with placebo exposure. A total of 56 treatment-emergent serious AEs (SAEs) were reported during the study. Of the 108 patients who received low-dose iTRE during the screening period, 9/108 (8.3%) experienced 10 treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs were acute respiratory failure (3/108 (2.8%)), according to the clinical judgement of the respective investigators, and COPD exacerbation (2/108 (1.9%)). For patients who received iTRE during the randomised treatment period, 17/66 (25.8%) patients experienced 26 treatment-emergent SAEs (table 3). The most frequently reported treatment-emergent SAE was COPD exacerbation, which occurred in 3/66 (4.5%) patients. For participants who received placebo, 6/58 (10.3%) patients experienced 20 treatment-emergent SAEs. The most frequently reported treatment-emergent SAEs were acute respiratory failure, which occurred in 3/58 (5.2%) patients, and acute myocardial infarction, which occurred in 2/58 (3.4%) patients (table 4).

There were six deaths overall (for three of which, death was the main cause of study discontinuation, two died after discontinuation but during follow-up), five in the randomisation phase in subjects assigned to iTRE and one death during the screening period in a subject who had received low-dose iTRE. None of the deaths were assessed as being related to study drug and 2/6 deaths occurred >7 days after the last dose of iTRE. A summary of the deaths is shown in table 5.

Termination of the study based on the DSMC's recommendation

On 15 September 2022, the DSMC recommended the study be terminated based on the totality of evidence supporting an unfavourable balance of a positive benefit to risk, concerns about slow study recruitment and a high degree of missing data for the primary end-point. The DSMC noted strong evidence that iTRE increased the risk of SAEs, severe AEs and AEs leading to initial or prolonged hospitalisations, and suggestive evidence of an increased risk of mortality. The DSMC noted that the changes in 6MWD in Treatment Period 1 and Treatment Period 2 were numerically worse with iTRE exposure than with placebo exposure, although the DSMC acknowledged that the Treatment Period 2 6MWD data would not be considered in the final analysis since the study switched to the contingent parallel design. Therefore, the study was terminated by the sponsor based on the DSMC's recommendation.

Post hoc *analysis*

An adverse response on active treatment had an incidence of 36.4% (24/66) compared to 27.6% (16/58) on placebo. There was no evidence to suggest that hyperinflation, occult heart failure or bronchospasm played any role in the untoward outcomes of the study (supplementary figures S5–S7). The patients who died during the study all had baseline diffusing capacity of the lung for carbon monoxide (D_{LCO}) ⩽25% predicted (supplementary figure S8). Evidence of a potential response was seen in 10.6% (7/66) of the

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TABLE 1 Baseline demographics and clinical characteristics of the study population

	Original crossover (n=64)					Contingent parallel (n=12)		
	iTRE		Placebo		Total (n=64)	iTRE (n=6)	Placebo (n=6)	Total (n=12)
	Treatment Period 1 (n=32)	Treatment Period 2 (n=29)	Treatment Period 1 (n=32)	Treatment Period 2 (n=26)				
Age (years)	68.7±8.1	66.9±7.6	66.5±7.6	68.0±8.3	67.6±7.8	70.3±6.7	73.3±2.2	71.8±5.0
Sex								
Male	19 (59.4)	12 (41.4)	14 (43.8)	16 (61.5)	33 (51.6)	6 (100.0)	4 (66.7)	10 (83.3)
Female	13 (40.6)	17 (58.6)	18 (56.3)	10 (38.5)	31 (48.4)	0	2 (33.3)	2 (16.7)
Race								
White	25 (78.1)	19 (65.5)	22 (68.8)	22 (84.6)	47 (73.4)	5 (83.3)	4 (66.7)	9 (75.0)
Black	7 (21.9)	8 (27.6)	8 (25.0)	4 (15.4)	15 (23.4)	1 (16.7)	2 (33.3)	3 (25.0)
Multiple	0	2 (6.9)	2 (6.3)	0	2 (3.1)	0	0	0
Ethnicity								
Hispanic or Latino	2 (6.3)	0	0	2 (7.7)	2 (3.1)	0	2 (33.3)	2 (16.7)
Not Hispanic or Latino	30 (93.8)	29 (100.0)	32 (100.0)	24 (92.3)	62 (96.9)	6 (100.0)	4 (66.7)	10 (83.3)
BMI ($kg \cdot m^{-2}$)	30.5±5.9	29.1±6.5	29.0±6.2	31.0±6.0	29.6±6.1	26.3±4.8	26.5±4.1	26.3±4.3
Age at time of WHO Group 3 PH-COPD diagnosis								
<63 years	7 (21.9)	10 (34.5)	12 (37.5)	7 (26.9)	19 (29.7)	1 (16.7)	0	1 (8.3)
⩾63– <69 years	9 (28.1)	7 (24.1)	7 (21.9)	6 (23.1)	16 (25.0)	3 (50.0)	0	3 (25.0)
⩾69– <75 years	8 (25.0)	6 (20.7)	7 (21.9)	7 (26.9)	15 (23.4)	0	4 (66.7)	4 (33.3)
⩾75 years	8 (25.0)	6 (20.7)	6 (18.8)	6 (23.1)	14 (21.9)	2 (33.3)	2 (33.3)	4 (33.3)
Borg dyspnoea score	5.48±2.8	4.62±2.5	4.63±2.4	5.48±3.1	5.1±2.6	3.08±1.9	5.17±1.6	4.1±2.0
6MWD (m)	213.6±84.9	215.1±79.2	226.1±87.9	219.8±80.0	219.8±86.0	231.5±60.8	259.2±84.2	245.3±71.5
Oxygen use (yes)	26 (81.3)	26 (89.7)	28 (87.5)	22 (84.6)	54 (84.4)	5 (83.3)	5 (83.3)	10 (83.3)
mPAP (mmHg)	43.6±11.2	43.8±10.9	43.5±10.7	44.2±11.3	43.5±11.0	36.0±5.2	34.0±6.1	35.0±5.6
PVR ($mmHg \cdot min \cdot L^{-1}$)	7.0±3.1	7.8±4.0	7.7±4.0	7.0±3.3	7.4±3.6	5.2±0.6	7.2±4.1	6.2±2.4
PCWP (mmHg)[#]	13.2±5.4	11.6±2.6	11.5±2.5	14.0±5.2	12.35±4.0	11.0±3.0	11.0±4.2	11.0±3.6
Plasma NT-proBNP ($ng \cdot L^{-1}$)	746.5±897.5	1570.3±2986.0	1513.6±2853.0	768.0±958.2	1130.0±2132.8	1701.3±2166.3	435.5±442.7	1068.4±1630.7
FVC (L)	2.8±0.9 (2.6)	2.5±1 (2.1)	2.5±1 (2.3)	2.8±0.9 (2.6)	2.7±1 (2.5)	3±0.7 (2.8)	2.6±0.7 (2.7)	2.8±0.7 (2.7)
FVC (% pred)	79.8±22.1 (77)	72.1±20.6 (69)	72.7±19.7 (70)	76.4±19.2 (77)	76.2±21 (76)	72.5±16.3 (73.5)	77.2±20.2 (75.5)	74.8±17.6 (73.5)
FEV_1 (L)	1.3±0.4 (1.3)	1.1±0.5 (1.1)	1.2±0.5 (1.2)	1.4±0.4 (1.3)	1.3±0.5 (1.2)	1.3±0.6 (1.1)	1.1±0.5 (1.0)	1.2±0.5 (1.0)
FEV_1 (% pred)	49.7±14.8 (48.0)	43.5±17 (39.0)	44.4±16.6 (42.5)	49.2±14.2 (49.0)	47±15.9 (45.0)	41.2±19.8 (38.5)	44±18.7 (42.0)	42.6±18.4 (42.0)
FEV_1/FVC (%)	48.3±10.8 (51.3)	46.4±13.6 (43.7)	47±13.3 (43.7)	49.8±10.7 (54.0)	47.6±12.1 (47.1)	41.1±12 (41.2)	42±13.8 (40.6)	41.6±12.3 (40.6)
D_{LCO} ($mmol \cdot min^{-1} \cdot kPa^{-1}$)	7±3.3 (6.3)	6.8±2.9 (6.9)	6.8±2.9 (6.9)	7.4±3.4 (6.4)	6.9±3 (6.5)	8.9±2.1 (9.9)	6.3±4 (5.6)	7.8±3.2 (6.9)
D_{LCO} (% pred)	29.3±13.8 (25.0)	30.3±13.4 (27.0)	30.3±13.7 (27.0)	31.2±14.6 (26.0)	29.8±13.7 (26.0)	32.8±4.8 (34.0)	27.5±19.1 (22.0)	30.4±12.5 (30.0)

Data are presented as mean±SD, n (%) or mean±SD (median). iTRE: inhaled treprostinil; BMI: body mass index; WHO: World Health Organization; PH: pulmonary hypertension; 6MWD: 6-min walk distance; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: two patients had left ventricular end-diastolic pressure <15 mmHg that qualified them for inclusion.

TABLE 2 6-min walk distance (6MWD) (week 12) for the full analysis set

	Original crossover		Contingent parallel	
	iTRE (n=60)	Placebo (n=52)	iTRE (n=6)	Placebo (n=6)
Baseline[#]				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	222.71±77.80	228.60±75.21	232.33±85.29	277.50±76.97
Median	234.00	242.50	268.00	293.00
Minimum[¶]–maximum	64.0–396.0	78.0–358.0	135.0–294.0	180.0–344.0
Week 12[+]				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	218.24±74.29	223.45±87.22	252.67±42.16	296.00±81.01
Median	224.00	233.50	276.00	289.50
Minimum–maximum	61.0–373.0	43.0–416.0	204.0–278.0	217.0–388.0
Change from baseline[§]				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	−4.47±39.01	−5.14±50.71	20.33±116.99	18.50±42.49
Median	0.00	0.00	8.00	24.50
Minimum–maximum	−85.0–78.0	−176.0–124.0	−90.0–143.0	−35.0–60.0

iTRE: inhaled treprostinil. [#]: baseline is defined as the last non-missing value preceding the start of treatment; [¶]: there were a few patients who had a drop in their 6MWD between screening and baseline visits such that their baseline 6MWD values were below the inclusionary lower limit; [+]: includes study week 12 of blinded treatment by study treatment; [§]: change from baseline=post-baseline value−baseline value.

patients who received iTRE. In the placebo group, there were two participants (3.4%) who demonstrated a "treatment response" by the same criteria. Patients who had evidence of a treatment response had a baseline mPAP ⩾40 mmHg and FEV_1 ⩾40% predicted. Interestingly, there were eight patients who died within 3 months after drug withdrawal in the OLE study at a median (range) time of 9 (1–91) days (supplementary table S9). Of these patients, 7/8 had a baseline mPAP >40 mmHg and 6/8 had a baseline PVR >7 WU.

Discussion

The PERFECT study of iTRE for PH-COPD is one of the largest randomised, controlled studies in PH-COPD to date. However, the study did not show evidence of a positive benefit with iTRE, and an emerging unfavourable benefit–risk profile resulted in early termination of the study.

TABLE 3 Treatment-emergent adverse events (TEAEs): safety population

	Enrolled	Randomised	
	iTRE (run-in) (n=108)	iTRE[#] (blinded) (n=66)	Placebo (blinded) (n=58)
Total TEAEs	165	178	122
Subjects with ⩾1 TEAEs	67 (62.0)	47 (71.2)	38 (65.5)
SAEs	10	26	20
Subjects with ⩾1 SAEs	9 (8.3)	17 (25.8)	6 (10.3)
TEAEs related to study treatment	115	77	32
Subjects with ⩾1 TEAEs related to study treatment	48 (44.4)	29 (43.9)	15 (25.9)
TEAEs leading to treatment discontinuation	15	11	6
Subjects with ⩾1 TEAEs leading to treatment discontinuation	11 (10.2)	8 (12.1)	3 (5.2)
TEAEs leading to study discontinuation	24	14	12
Subjects with ⩾1 TEAEs leading to study discontinuation	16 (14.8)	10 (15.2)	2 (3.4)

Data are presented as n or n (%). iTRE: inhaled treprostinil; SAE: serious adverse event. [#]: number of subjects exposed to iTRE during 12-week blinded treatment period only, including washout period.

TABLE 4 Treatment-emergent adverse events (TEAEs) occurring in ⩾4% of the safety population

	Enrolled	Randomised	
	iTRE (run-in) n=108	iTRE[#] (blinded) n=66	Placebo (blinded) n=58
Total TEAEs	165	178	122
Subjects with ⩾1 TEAEs	67 (62.0)	47 (71.2)	38 (65.5)
System organ class/preferred term			
Gastrointestinal disorders	13 (12.0)	9 (13.6)	8 (13.8)
Nausea	2 (1.9)	3 (4.5)	1 (1.7)
General disorders and administration site conditions	14 (13.0)	15 (22.7)	6 (10.3)
Fatigue	2 (1.9)	7 (10.6)	2 (3.4)
Chest discomfort	3 (2.8)	5 (7.6)	0
Infections and infestations	6 (5.6)	10 (15.2)	13 (22.4)
Upper respiratory tract infection	1 (0.9)	2 (3.0)	4 (6.9)
Musculoskeletal and connective tissue disorders	4 (3.7)	6 (9.1)	9 (15.5)
Arthralgia	0	2 (3.0)	3 (5.2)
Jaw pain	0	1 (1.5)	3 (5.2)
Nervous system disorders	12 (11.1)	12 (18.2)	9 (15.5)
Headache	9 (8.3)	7 (10.6)	4 (6.9)
Dizziness	2 (1.9)	4 (6.1)	2 (3.4)
Respiratory, thoracic and mediastinal disorders	46 (42.6)	35 (53.0)	22 (37.9)
Dyspnoea	19 (17.6)	19 (28.8)	9 (15.5)
Cough	16 (14.8)	11 (16.7)	3 (5.2)
Oropharyngeal pain	9 (8.3)	3 (4.5)	2 (3.4)
Productive cough	5 (4.6)	4 (6.1)	2 (3.4)
COPD	5 (4.6)	6 (9.1)	4 (6.9)
Hypoxia	4 (3.7)	4 (6.1)	3 (5.2)
Throat irritation	5 (4.6)	3 (4.5)	0
Acute respiratory failure	3 (2.8)	0	3 (5.2)
Vascular disorders	4 (3.7)	5 (7.6)	1 (1.7)
Hypotension	0	4 (6.1)	1 (1.7)

Data are presented as n or n (%). iTRE: inhaled treprostinil. [#]: number of subjects exposed to iTRE during 12-week blinded treatment period only, including washout period.

The reasons for the lack of a positive treatment benefit remain unclear. Previous reports attest to the potential benefit of PH therapy in PH-COPD, although the only other randomised trial of tadalafil of comparable size was similarly negative [6, 14–17]. The design of the PERFECT study did enrich for a pulmonary vascular phenotype by having the haemodynamic threshold above the recognised definition of PH (mPAP ⩾30 mmHg and PVR ⩾4 WU). The patients had a diagnosis of COPD per the GOLD criteria and were required to have a baseline computed tomography scan to exclude fibrosis [12]. Similarly, the reason for the potential signal of a detriment in the study is also uncertain, given the otherwise strong safety profile in patients with PAH and PH-ILD [10, 18]. Our *post hoc* analysis did lend some insight in that those patients with D_{LCO} <25% predicted have a reduced likelihood of benefit and are at greater risk of mortality which may or may not be related to the PH therapy, while those PH-COPD patients with FEV_1 >40% predicted and mPAP >40 mmHg might be more likely to demonstrate benefit.

While the incidence of treatment-emergent AEs was relatively similar with both treatment exposures (iTRE 71.2% *versus* placebo 65.5%), the number of individuals who experienced a SAE was numerically greater with active treatment compared with placebo (25.8% *versus* 10.3%). AEs of cough, headache, hypotension, oropharyngeal pain, throat irritation and nausea are known side-effects of iTRE [9]. However, in the PH-COPD population evaluated here, a notable difference in select AEs between active and placebo occurred (*e.g.* dyspnoea (28.8% *versus* 15.5%) and fatigue (10.6% *versus* 3.4%)). Comparable differences between active and placebo for dyspnoea have not been previously reported in prior PAH and PH-ILD trials of iTRE [9–11, 18]. There was no discernible difference pertaining to change in supplemental oxygen flow rates between the two treatment arms during the course of the study. Specifically, 13% (10/76) of the participants reported a change in supplemental oxygen use; of these, five occurred during iTRE and five during placebo treatment. These changes were constituted by seven participants having an increased flow rate, while three decreased their flow rate.

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TABLE 5 Summary of patient deaths

Sex	Age (years)	Baseline 6MWD (m)	Cause of death	Study day	Days after last dose	Highest dose (breaths)	Relevant medical history	mPAP (mmHg)	PVR (mmHg·min·L^{-1})	PAWP (mmHg)	D_{LCO} (% pred)	FEV_1 (% pred)	FEV_1/FVC (%)
Male	80	121	Acute coronary syndrome at home	7	0	4	CAD (MI 2014), OSA, T2DM, atrial fibrillation	41	6.59	12	23	40	32.59
Male	55	121	Acute coronary syndrome, respiratory failure, right ventricular failure	126	29	12	Right heart failure, abdominal distension	35	12	3	19	27	55.17
Male	67	120	Hypoxic brain injury status post unwitnessed cardiac arrest at home	5	3	3	CHF, hepatic cirrhosis, chronic respiratory failure, severe anaemia	39	4.9	12	26	45	47.51
Female	68	110	Food aspiration leading to aspiration pneumonia	66	1	6	HIV, chronic hepatitis with cirrhosis, DM	37	5.8	7	14	67	67.55
Female	64	116	COPD exacerbation *versus* worsening PH	100	30	12	Bipolar I, asthma, pre-DM	40	6	12	14	73	44.3
Female	68	–[#]	Acute respiratory failure (sudden SOB at home, coded in ambulance)	NA	6	3	T2DM, asthma, OSA, atherosclerosis, CKD	46	7.5	11	27	44	66.89
Randomised subjects who did not die on study[¶]	NA	NA	NA	NA	NA	NA	NA	46 (30–65)	6.9 (4–16)	12 (5–30)	35 (9–79)[+]	46 (18–78)	47 (24–69)

6MWD: 6-min walk distance; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular pressure; PAWP: pulmonary arterial wedge pressure; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CAD: coronary artery disease; MI: myocardial infarction; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellites; CHF: congestive heart failure; PH: pulmonary hypertension; DM: diabetes mellites; NA: not applicable; SOB: shortness of breath; CKD: chronic kidney disease. [#]: no baseline value available (screening 6MWD was 132 m); [¶]: data are presented as mean (minimum–maximum); [+]: screen fail.

Although the six deaths (two of these deaths were ⩾4 weeks after the last dose) during the study were not judged to be attributed to the drug by the respective study investigators at the time of reporting, it is notable that all of these were patients who received iTRE (table 5). Two deaths (and potentially three, as one was an unwitnessed cardiac arrest) were attributed to acute coronary syndrome [10, 18].

There are multiple limitations to this study. One of the DSMC's concerns was the slow rate of study recruitment, possibly due to limited PH diagnosis in the COPD population. The slow recruitment was further aggravated by the onset of the COVID-19 pandemic. On 20 March 2020, COVID-19 resulted in a pause in screening and an overall pause in study activity on 16 April 2020. As such, patients on treatment as of 13 March 2020 were missing key protocol-required data, especially for the primary end-point of 6MWD (which required onsite assessment). There were minor modifications to the inclusion and exclusionary criteria during the study to optimise recruitment; notably, enrolment was increasing at study termination with abatement of the pandemic and as more sites became operational. Unfortunately, imaging of the chest was not collated for this study and therefore we were unable to evaluate the radiographic extent and nature of the emphysema.

In conclusion, the results of this study indicated that patients receiving iTRE experienced numerically more events for AEs, SAEs, deaths, treatment discontinuations and study discontinuations compared with placebo. In addition, patients treated with iTRE showed no improvement in 6MWD when compared with placebo. Overall, this study showed that the risks in treating PH-COPD patients with iTRE outweighed the potential positive benefits, thereby justifying its early termination. The results of this study should not impede further investigations of PH-COPD treatments. Indeed, it is the hope of the authors and the sponsor that there will be lessons learned from this study that help lay the foundation for future successful clinical trial designs to meet the large unmet medical need of PH-COPD.

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Data availability: Data may be made available to *bona fide* researchers who agree to comply with patient-informed consent and submit a research proposal form *via* www.utcrequests.com. Proposals will be evaluated by the sponsor and data will be made available once the research proposal has been approved and the data sharing agreement between sponsor and investigator signed.

Ethics statement: The study protocol was approved by the institutional review board at the respective participating sites and was monitored by an independent data and safety monitoring committee.

This clinical trial was prospectively registered at ClinicalTrials.gov with identifier number NCT03496623.

Conflict of interest: S.D. Nathan is a paid consultant for United Therapeutics. R.G. Argula reports advisory board consulting fees from United Therapeutics, Liquidia Inc., Merck Pharmaceuticals, Janssen and Accordant Health (CVS), and lecture honoraria from United Therapeutics, outside the submitted work. M.G. Trivieri reports advisory board participation with Janssen, outside the submitted work. B. Medarov reports lecture honoraria from Jensen Pharmaceuticals, outside the submitted work. A. Raina reports lecture honoraria from Merck and United Therapeutics, outside the submitted work. M.G. Risbano reports grants from Shadyside Foundation, royalties from Springer (*Pulmonary Hypertension: Controversial and Emerging Topics*), and advisory board participation with Gilead and Liquidia, outside the submitted work. T. Thenappan reports grants from United Therapeutics, Aerovate, Merck and Aria CV, and consulting fees from Merck and United Therapeutics, outside the submitted work. J.S. Soto reports grants, lecture honoraria, travel support and advisory board participation with GlaxoSmithKline and Genentech Pharmaceuticals, outside the submitted work. H. Bell, V. Lacasse, P. Sista, M. Di Marino, A. Smart, B. Hawkes and E. Nelson are employees of United Therapeutics, the PERFECT study sponsor. T. Bull reports grants from Bayer, Merck, Insmed and Aerovate, lecture honoraria from Merck, payment for expert testimony from Lung Biotechnology, travel support from Lung, advisory board participation with Keros, consultancy for United Therapeutics and a leadership role as PHA SLC chair, outside the submitted work. V. Tapson is a paid consultant for United Therapeutics. A. Waxman reports grants from Aria CV PI, AI Therapeutics and Acceleron/Merck, consultancy for United Therapeutics, and data and safety monitoring board participation with Insmed, outside the submitted work. The remaining authors have no potential conflicts of interest to disclose.

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