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RESEARCH ARTICLE

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COPD associated pulmonary hypertension: A post hoc analysis of the PERFECT study

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Abstract

The PERFECT study, a randomized, controlled, double-blind study of inhaled treprostinil in patients with COPD and associated pulmonary hypertension (PH-COPD) was a negative trial that was terminated early. The reason(s) for the negative outcome remains uncertain. A post hoc analysis of data from the PERFECT study was undertaken to identify adverse responders and possibly potential responders. The goal was also to provide insight into phenotypes for possible inclusion and exclusion in future PH-COPD clinical trials. An adverse response on active treatment was seen in 36.4% (24/66) of the subjects compared to 27.6% (16/58) on placebo. There was no evidence to suggest that hyperinflation, bronchospasm, or occult heart failure played any role in the untoward outcomes of the study. The patients who died during the study all had baseline diffusing capacity for carbon monoxide ≤25% of predicted. Evidence of a potential response was seen in 10.6% (7/66) of the patients who received inhaled treprostinil. Patients who had evidence of a treatment response had a baseline mean pulmonary artery pressure of ≥40 mmHg and a forced expiratory volume in the first second of ≥40%. Change in N-terminal prohormone of brain natriuretic peptide did not predict clinical response. This post hoc analysis provides information that may potentially enable improved selection of patients for future therapeutic trials in PH-COPD. These analyses are post hoc, observational, and exploratory. The thresholds defining the spectrum of responders are preliminary and may require further refinement and validation in future studies.

KEYWORDS
double-blind method, chronic obstructive, hypertension, pulmonary, pulmonary disease, treprostinil

ClinicalTrials.gov ID: NCT03496623

Steven D. Nathan and Victoria Lacasse contributed equally to this study.

The PERFECT study (NCT03496623), a randomized, double-blind trial, examined the efficacy of inhaled treprostinil (iTRE) in patients with pulmonary hypertension due to chronic obstructive pulmonary disorder (PH-COPD). The study was negative based on an unfavorable risk-benefit balance and was stopped early at the recommendation of the Data Safety and Monitoring Committee.[1] In addition to a lack of observed efficacy, there were a high number of safety events, which was not due to a specific event or follow any particular pattern. The purpose of the current analyses was to glean any insights from this trial that might inform the design of future studies for PH-COPD treatments.

Details of the PERFECT clinical trial design have been described in detail previously.[1] The major hemodynamic inclusion criteria for the study included a mean pulmonary artery pressure (mPAP) of ≥30 mmHg and a pulmonary vascular resistance (PVR) of ≥4 Wood units (WU), together with a pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg. These thresholds intended to enrich the study for a pulmonary vascular phenotype with the pretest hypothesis that if there was sufficient hemodynamic impairment, then clinical improvement might result no matter the severity of the underlying COPD. Specifically, there was no lower limit to the forced expiratory volume in the first second (FEV1) or diffusing capacity for carbon monoxide (DLCO). The most severe PH-COPD patients were ruled out through other entry criteria regarding supplemental oxygen (resting saturation ≥90% during screening with or without supplemental oxygen and supplemental oxygen ≤10 L/min) and 6-minute walk distance (6MWD; ≥100 m). The study also included baseline imaging to exclude morphologies such as combined pulmonary fibrosis and emphysema. The study initially had a double-blind cross-over design, such that patients had two 12-week periods of blinded treatment with a 2-week washout period. However, a prespecified blinded interim analysis revealed that ≥15% of the primary endpoint data at Week 25 was missing, which triggered a switch from the crossover design to a parallel design to shorten the duration of the study and improve patient retention (Figure 1).

Despite the PERFECT study being a negative study, it is important to identify those who had an adverse response, while conversely, it is also conceivable that there might be a small group of patients who potentially responded to the therapy. To gain further insight, several exploratory analyses were undertaken. The questions posed while scrutinizing the primary data included whether there were certain baseline characteristics that could help define a nonresponder group that drove the negative efficacy outcome. The steering committee and the sponsor opted to explore several possible reasons that could explain or contribute to the negative results of the study. These included the enrollment of patients who were more ventilatory limited rather than having a pulmonary vascular limitation. With an elderly population

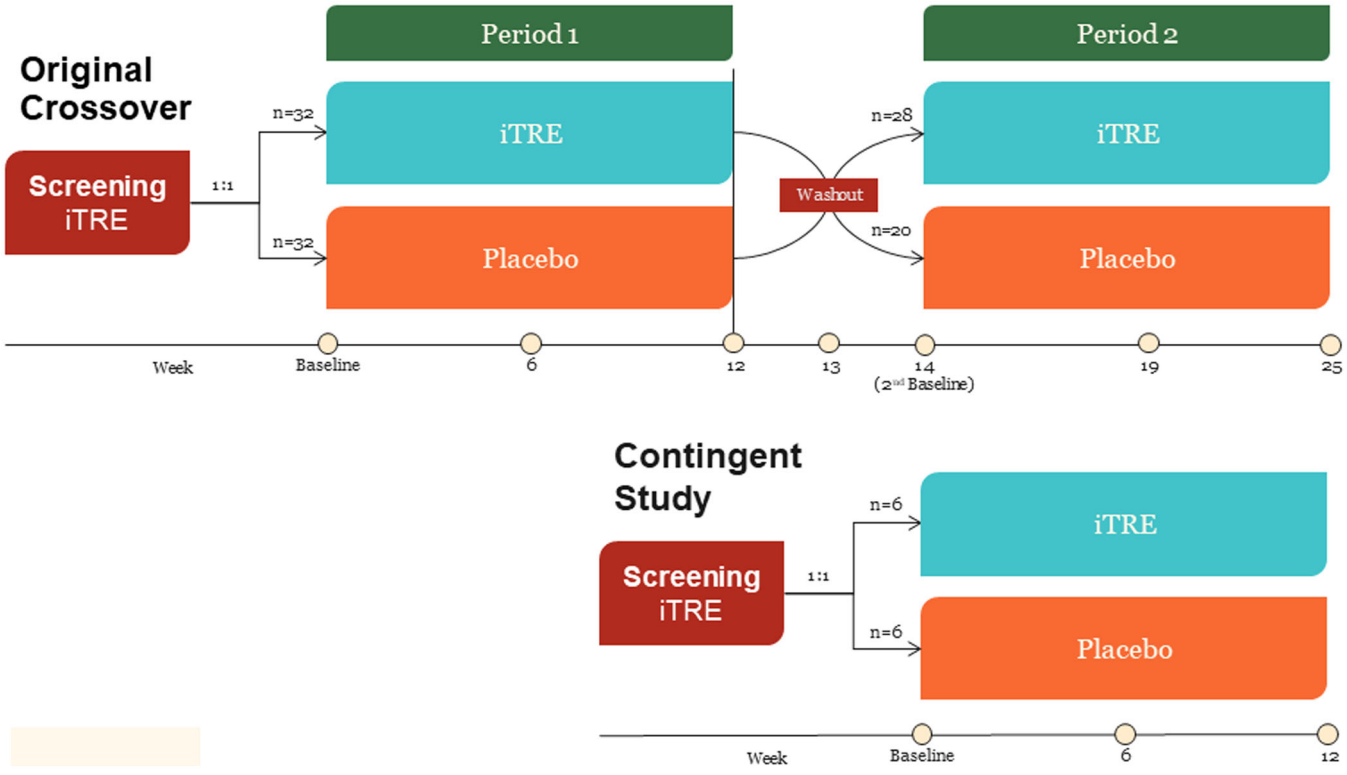

FIGURE 1 Study design (reproduced with permission from the *European Respiratory Journal*). ITRE, inhaled treprostinil.

and the likelihood of comorbidities, it is also conceivable that iTRE might have unmasked occult heart failure with preserved ejection fraction (HFpEF) in some patients. Being that these patients had obstructive airway disease, it is possible that iTRE might have induced bronchospasm in some of the patients. We also explored whether there is an inflection point beyond which there is so much vascular dropout that vasodilating the remaining vasculature could be deleterious. On the other end of the spectrum, it is conceivable that there might be a small group of patients who potentially responded to the therapy and could be a target group for future research in this patient population.

In this manuscript, we report the results of various post hoc analyses of the PERFECT study. It should be noted that these analyses were not prespecified and should be regarded as hypothesis-generating and therefore exploratory.

METHODS

The PERFECT study was a multicentre, randomized, double-blind, placebo-controlled trial to evaluate if iTRE improved the primary endpoint of placebo-corrected change in 6MWD after 12 weeks compared with placebo. The study design is shown in Figure 1. The study protocol was approved by the institutional review board at the respective participating sites and allowed for post hoc analyses. The post hoc analyses in this manuscript were generated by the steering committee and the sponsor.

Several evaluations comparing responders to non-responders were made to discern potential underlying physiological mechanisms that could have led to the observed outcomes:

1. The role of hyperinflation is measured by the baseline residual volume to total lung capacity ratio (RV/TLC).
2. The role of occult HFpEF was evaluated through an analysis of the PCWP.
3. The role of possible worsened bronchospasm was examined through an analysis of patients who reported cough, dyspnea, or who had a decrease in their FEV1/forced vital capacity (FVC) ratio.
4. The role of excess vascular dropout was evaluated using the lowest baseline DLCOs as a surrogate.
5. Disease severity was further evaluated through a comparison of mPAP and PVR to FEV1.

Responder analyses

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 N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at either 6 or 12 weeks.[2] Since there were reports of patient deaths upon drug withdrawal after the termination of the open-label extension (OLE) study (RIN-PH-305), we also sought to define a distinct responder group by inferring response for those who succumbed after drug withdrawal.

Statistical analysis

As this was a post hoc analysis, all summary data are descriptive without any formal statistical comparisons.

RESULTS

All 76 randomized patients from the PERFECT study were included in this post hoc analysis. Of the 76 randomized patients, there were 24/66 (36.4%) who received iTRE and met criteria of an adverse response versus 16/58 (27.6%) in the placebo arm (three patients were adverse responders for both iTRE and placebo and were counted for both treatment conditions). In total, 7/66 (10.6%) patients received iTRE and met the criteria of a potential response versus 8.6% (5/58) in the placebo arm sequence (there was one patient who was a responder for both iTRE and placebo and was counted for both treatment conditions) (Table 1). Additionally, there were five patients who died during the randomized control trial (RCT) portion of the study during iTRE exposure. We focused our evaluations on only those

TABLE 1 Physiologic and haemodynamic characteristics of the responders as defined by a ≥15% increase in 6MWD accompanied by a ≥20% reduction in NT-proBNP.

FVC%	FEV1%	FEV1/FVC	TLC%	mPAP	PVR	PCWP
84	54	48	96	42	8	10
78	59	59	68	57	5	14
89	69	56	-	63	16	14
100	44	33	132	57	8.8	15
80	79	67	91	46	12	10
63	42	51	88	55	15	9
62	39	47	92	62	12	14

Abbreviations: 6MWD, 6-min walk distance; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TLC, total lung capacity.

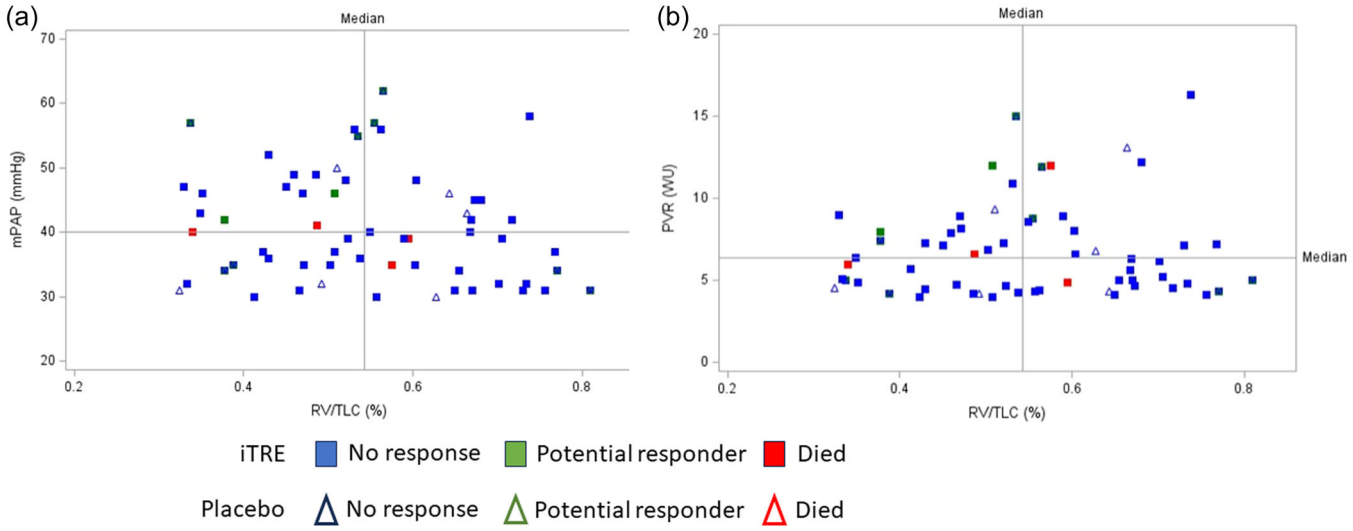

FIGURE 2 X–Y plots of RV/TLC% to mPAP (a) and PVR (b) based on treatment assignment, response, and mortality for both groups. FEV1, forced expiratory volume in 1 s; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RV/TLC, residual volume to total lung capacity; WU, wood units.

treated with iTRE to discern possible reasons for any treatment effect (beneficial or adverse).

What was the role of hyperinflation in terms of response and mortality?

An X–Y plot of RV/TLC% to mPAP and PVR based on treatment assignment, response, and mortality is shown in Figure 2a,b. Visual inspection of this plot reveals no discernible patterni mplicating a role for hyperinflation in terms of response and mortality.

Did iTRE unmask occult HFpEF?

An X–Y plot of the PCWP to FEV1% color-coded by a 20% increase or decrease in the NT-proBNP shows no discernible pattern (Figure 3). The scatterplot demonstrates increases and decreases in NT-proBNP occurring across the spectrum of baseline PCWP. Interestingly, the patients who succumbed during the study were not on the high end of the eligible baseline PCWP (Figure 4a,b).

Did bronchospasm play any role?

Overall, 19 (29%) and 11 (17%) patients reported dyspnea or cough while exposed to iTRE, respectively, compared to 9 (16%) and 3 (5%) on placebo. Spirometry was recorded at baseline and Weeks 6 and 12. There were 31 patients who had a decrease in their FEV1/FVC ratio of ≥3% between their baseline spirometry and Week 6 spirometry, 20 on iTRE, and 11 on placebo (there were eight patients who had a decrease on both iTRE and placebo). A scatterplot of DLCO% to mPAP color-coded by those who had a ≥ 3% drop in their FEV1/FVC ratio also does not have a discernible pattern or distinct clustering (Figure 5). Week 12 spirometry was not evaluated due to significant missing data.

Did vascular dropout play a role?

The percent predicted DLCO (a surrogate for the residual pulmonary vasculature) shows that all patients who died had a DLCO% predicted <25% and all treatment responders had a baseline DLCO% predicted higher than 25% (Figure 6a).

Hemodynamic and lung function predictors of response

All iTRE responders had a baseline mPAP >40 mmHg (see Figure 6a), and a higher than median PVR (see Figure 6b). Visual inspection of X–Y plots of DLCO% predicted by mPAP (Figure 5a), DLCO% by PVR (Figure 6b), and FEV1% by DLCO (Figure 6c) attest to the treatment responders having a mPAP >40 mmHg, PVR > 7 WU, and FEV1 > 40% predicted.

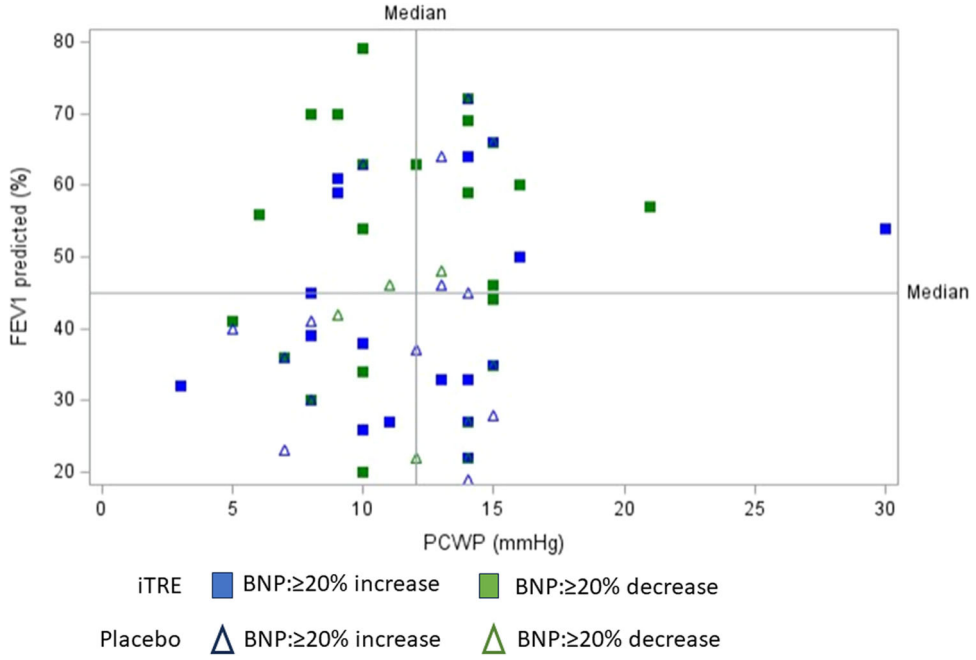

FIGURE 3 X–Y plot of the PCWP to FEV1%, color-coded by a 20% increase or decrease in NT-proBNP at Week 6 for both groups. FEV1, forced expiratory volume in 1 s; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure. Reproduced and modified with permission from the *European Respiratory Journal*.

Did change in NT-proBNP predict response in 6MWD?

Of the patients who received iTRE, 28.8% (19/66) showed a decrease of ≥20% in NT-proBNP from baseline to Week 6. Within the 19 patients who experienced a reduction in NT-proBNP, 26% (5/19) also demonstrated an increase of ≥15% in 6MWD at 6 weeks. Among the 47 patients who did not have a reduction in NT-proBNP while on iTRE through 6 weeks, 12.8% (6/47) still exhibited an increase of ≥15% in 6MWD. Overall, out of the 66 randomized patients who received iTRE, 16.7% (11/66) recorded an increase of ≥15% in 6MWD. Among these 11 patients, only 45% (5/11) also had a reduction of ≥20% in NT-proBNP at 6 weeks.

Defining response by death with withdrawal of drug (during OLE)

There were eight patients who died within 3 months after drug withdrawal at a median time of 9 days (range: 1–91 days; see Table 2). Of these patients, 7/8 had a baseline mPAP >40 mmHg and 6/8 had a baseline PVR > 7 WU. Of these eight patients, three were responders to iTRE while receiving the drug (as defined by a 15% increase in 6MWD + a 20% decrease in NT-proBNP). An additional patient had a >20% decrease in their NT-proBNP while receiving the drug but without the 15% improvement in 6MWD.

Assessing potential response across the RCT as well as the OLE, there were seven potential responders in the RCT and eight who died after drug withdrawal in the OLE (three patients were deemed responders in both studies). Therefore, the proportion of patients, as calculated by response on active treatment and/or response defined by withdrawal, equates to a potential response rate of 18.2% (12/66). A comparison of the baseline characteristics of potential responders and adverse responders while receiving iTRE is shown in Table 3. Cough or dyspnea was reported in 58% of adverse responders (14/24) and 16% of responders (2/12).

DISCUSSION

There have been few randomized, placebo-controlled trials for PH-COPD and those to date have focused mostly on the diagnostic modality and the hemodynamic threshold to define PH, but have largely been agnostic to the underlying lung physiology.[3–5] Even though the PERFECT study was stopped early, it can still provide a wealth of data that may help identify responders or important subgroups for future PH-COPD trials. The purpose of this post hoc analysis was to determine if there are lessons that could be applied to

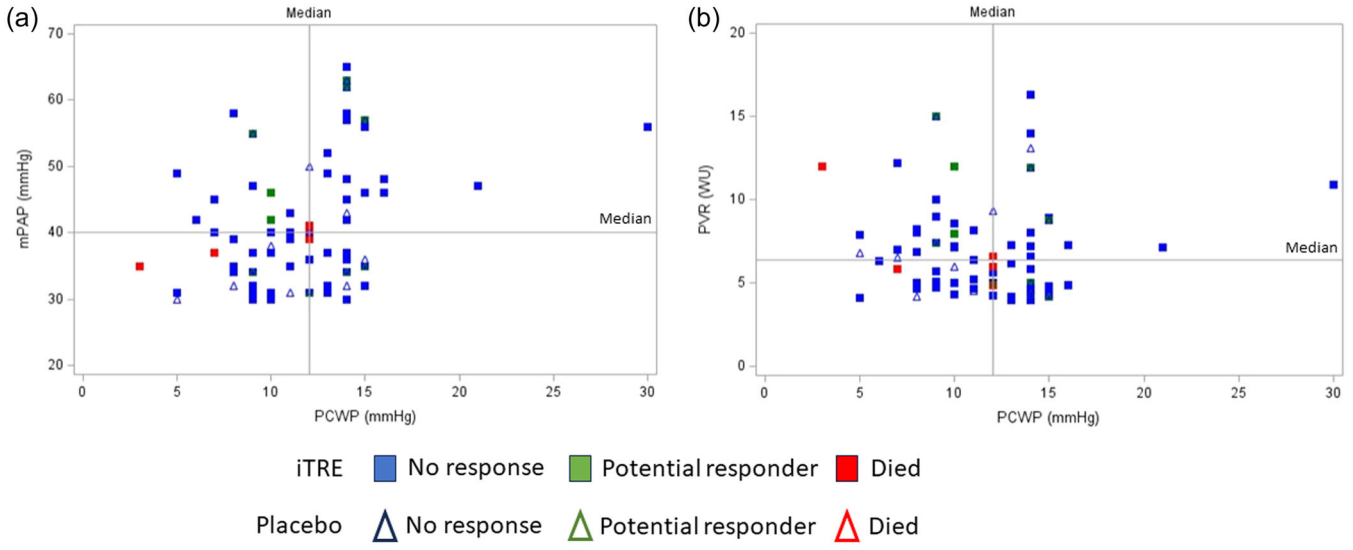

FIGURE 4 X–Y-plot, color-coded base on response, of (a) PCWP to mPAP; and (b) PCWP to PVR for both groups. The patients with PCWPs >15 mmHg had left ventricular diastolic pressure measurements ≤15 mmHg which qualified them for the study. mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

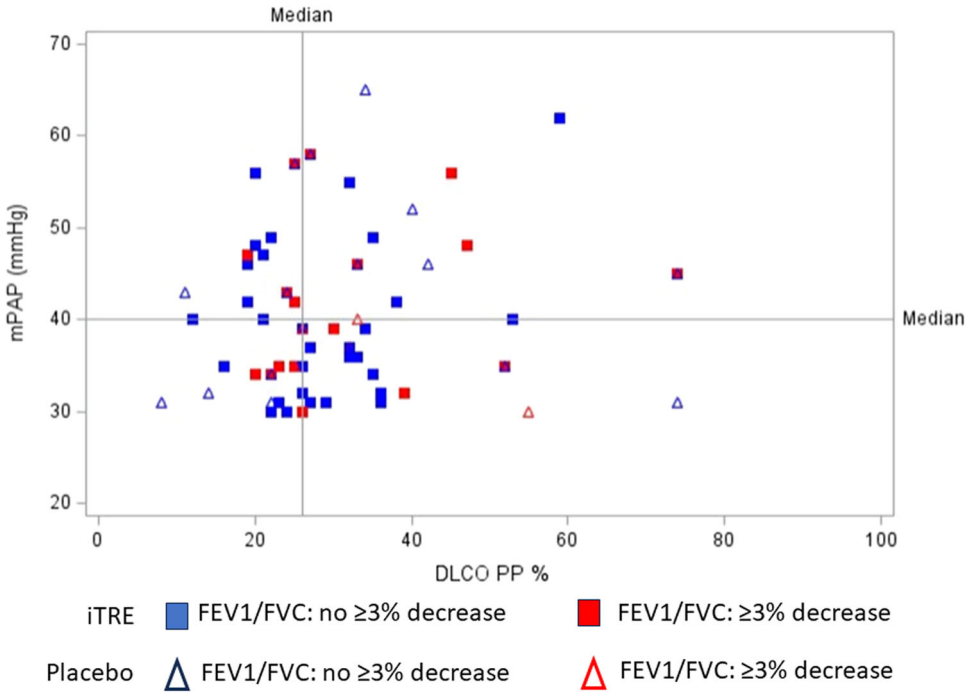

FIGURE 5 X–Y-plots of DLCO% to mPAP, color-coded by those who had a ≥3% drop in their FEV1/FVC for both groups. DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; PP, percent predicted. Reproduced and modified with permission from the *European Respiratory Journal*.

future clinical trials for this difficult disease state by exploring how best to mitigate risk. Future trials can be enriched by identifying PH-COPD patients in whom therapy might be deleterious or unlikely to benefit and identifying phenotypes that might be primed for a salutary response.

Before the PERFECT study, there was an existing large body of evidence to support the implementation of clinical trials for PH-COPD.[3,5] Therefore, the negative outcome of the PERFECT study should not be misconstrued to infer that the treatment of PH-COPD is not possible. Indeed, there are numerous examples of

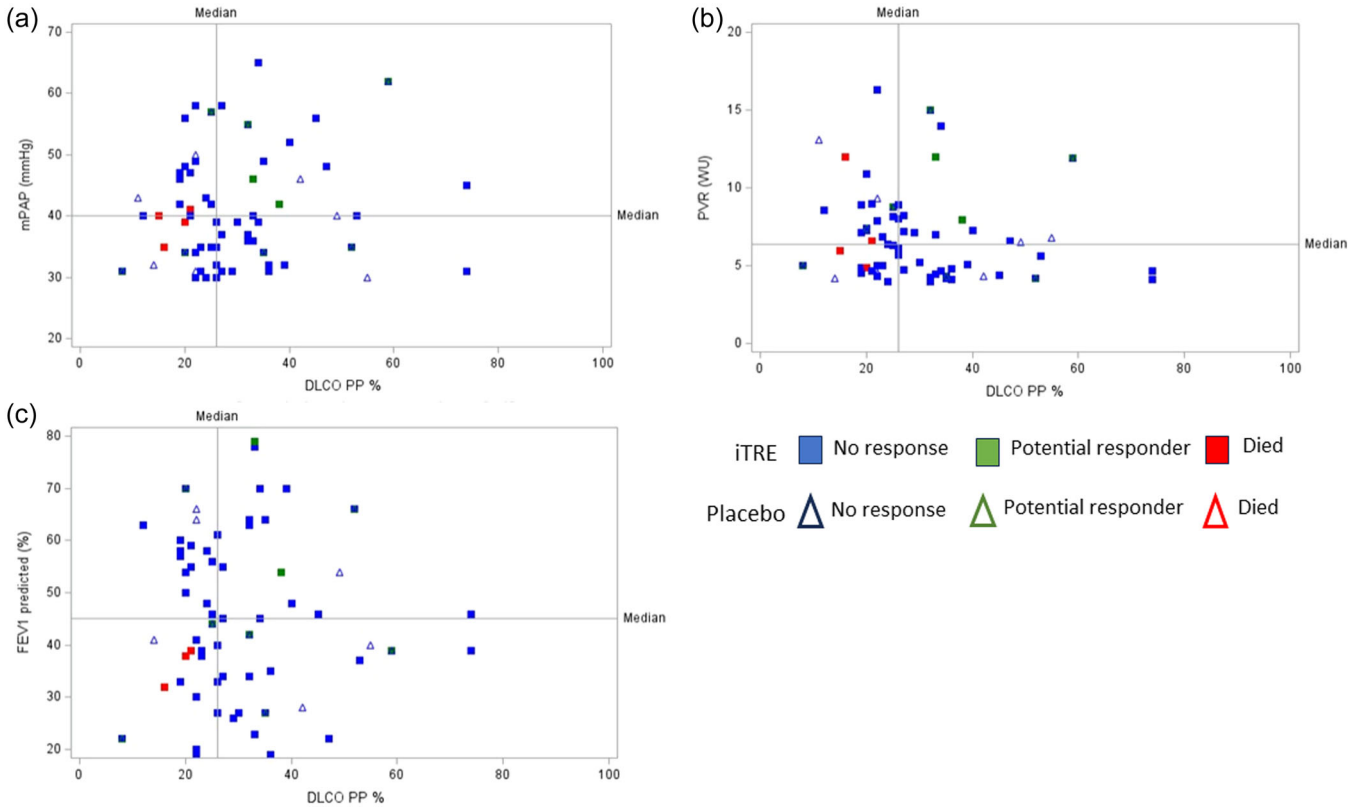

FIGURE 6 X–Y-plots, color-coded based on response, of (a) DLCO% to mPAP; (b) DLCO% to PVR; (c) DLCO% to FEV1% for both groups. DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; mPAP, mean pulmonary arterial pressure; PP, percent predicted; PVR, pulmonary vascular resistance.

negative and even harmful clinical trials being followed by positive studies for the same disease state. Nowhere is this more evident than in the RISE-IIP study of patients with PH and interstitial lung disease (PH-ILD), which showed that treatment with riociguat was harmful but which was subsequently followed by the positive INCREASE study with iTRE.[6,7]

The most widely accepted serum biomarker in PH clinical trials which has also found utility in COPD is the NT-proBNP.[8] It was, therefore, interesting to note that 28% of the study participants had a 20% reduction in NT-proBNP. Presumably, therefore, iTRE was reducing right ventricular strain in these patients. However, this biochemical effect did not translate to a discernible 6MWD clinical benefit. Specifically, the 20% decrease in NT-proBNP did not appear to predict improvement in 6MWD, although it is unknown if a longer period of drug administration may have eventually resulted in clinical benefit.

While a difference in outcomes in PH-ILD was demonstrated over a 16-week period in the INCREASE study, it should be borne in mind that the prognosis of PH-ILD is distinctly worse than PH-COPD.[7,9–12] While clinical improvement or a slower disease progression is anticipated with an intervention, in many situations, the difference in outcomes is driven by the rate of deterioration in the placebo arm. Therefore, it might be reasonable to speculate that a longer period of time may be necessary for PH-COPD trials to enable a clinical benefit to fully manifest.

The patients who appeared to respond to therapy based on our composite improvement metric (≥15% increase in 6MWD + ≥ 20% decrease in NT-proBNP) all had a mPAP ≥40 mmHg, FEV1 > 40% of predicted and DLCO > 25% of predicted. Interestingly, there were two patients on placebo whose mPAPs were below the "40/40" FEV1 and mPAP thresholds who qualified as responders. This attests to the imperfection and need for further refinement of our thresholds and underscores the potential variability in 6MWD and NT-proBNP. Interestingly, a mPAP of >40 mmHg is more often associated with PAH patients than those with PH-COPD, suggesting that perhaps some COPD patients share phenotypic characteristics with Group 1 PH. There was no discernible pattern to those who were deemed "responders by death" after drug withdrawal in the OLE study. Notably, only 50% of these (4/8) manifest any evidence of clinical response while on active drugs. Therefore, our definition of response to treatment does not appear to capture all patients who might derive benefit.

TABLE 2 Characteristics of responders in the OLE as defined by death after drug withdrawal.

FVC %	FEV1%	TLC %	FEV1/FVC %	mPAP	DLCO %	PVR	PCWP	Responder (NT-proBNP + 6MWD)	NT-proBNP responder	Death after last dose (days)	# of days in 305 study	% change in NT-proBNP in 6 weeks
89	78	105	67	36	33	4.4	14	No	No	91	810	−33
54	45	-	64	65	34	14.0	14	No	No	1	318	-
78	59	68	59	57	30	5.0	14	Yes	Yes	90	1383	−35
62	39	92	47	62	59	12.0	14	Yes	No	9	1164	−42
89	69	-	56	63	-	16.3	14	Yes	Yes	1	638	−50
56	17	95	23	43	11	13.1	14	No	No	9	21	-
69	36	119	38	45	-	12.2	7	No	Yes	6	40	-
68	50	79	55	48	20	7.3	16	No	Yes	84	365	-

Note: Baseline data or screening data (if baseline unavailable).

Abbreviations: DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLE, open-label extension; PCWP, pulmonary capillary wedge pressure; PP, percent predicted; PVR, pulmonary vascular resistance; TLC, total lung capacity.

TABLE 3 Comparison of baseline characteristics between "responders" and adverse responders on iTRE.

	Potential responders on iTre		Adverse responders on iTre		
	N = 12	Mean (SD)	*N* = 24	Mean (SD)	*p* Value
FVC% *N* (mean)	12	74.3 (14.5)	23	78.6 (26.9)	0.5500
FEV%	12	51.0 (18.1)	23	46.5 (16.4)	0.4592
FEV1/FVC%	12	50.9 (13.7)	23	46.1 (10.7)	0.2634
TLC (L)	10	6.0 (1.6)	18	6.1 (2.0)	0.8179
DLCo%	9	31.7 (13.2)	21	25.4 (10.2)	0.1679
mPAP (mmHg)	12	51.6 (9.5)	24	41.6 (8.1)	0.0022
PVR	12	10.7 (3.9)	24	6.9 (2.3)	0.0071
PCWP	12	12.6 (2.8)	23	11.6 (5.4)	0.4684
6MWD	12	157.8 (47.6)	24	201.1 (82.5)	0.1028
NT-proBNP	12	3601.8 (3925.2)	23	700.7 (985.0)	0.0273

Abbreviations: 6MWD, 6 min walk distance; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; iTRE, inhaled treprostinil; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TLC, total lung capacity.

There were no responders with RV/TLC ratios >60%. It is possible that these patients were more ventilatory limited and therefore could not satisfy the 15% increase in 6MWD to be regarded as responders. Therefore, an RV/TLC ratio >60% might be a reasonable threshold as an exclusionary criterion to enrich future PH-COPD studies. There were 31/76 patients (20 receiving iTRE; 11 on placebo) who had a ≥ 3% reduction in their FEV1/FVC ratio, perhaps indicating an element of bronchospasm in this population.

A reasonable approach in future clinical trials of inhaled PH therapies for PH-COPD is to have a run-in period to ensure tolerability and rule out any element of bronchospasm that could adversely impact the study. In addition, an acute bronchodilator response or high baseline eosinophil count could be alternate strategies to rule out such patients. However, there is data to suggest that COPD patients with high eosinophils could be at higher risk of PH and one danger for future PH-COPD clinical trials is to make the entry criteria too restrictive, thus hindering recruitment.[13]

Our analysis of response based on the PCWP did not reveal any pattern to suggest that HFpEF played any role in the worsened outcomes noted. Arguably, the PCWP is not the best surrogate for HFpEF especially considering that an accurate PCWP can be difficult to obtain in COPD patients coupled with variability and controversy in how best to measure the tracing.[14] Unfortunately, echocardiographic data was not collected for this study, and therefore, we cannot rule out that occult HFpEF might have been unmasked in some of the cases.

A notable observation is that all the patients who succumbed during the course of the study had a baseline DLCO < 25% of predicted. DLCO can be regarded as a surrogate for the functional pulmonary vascular bed and therefore this raises the notion that perhaps there is an inflection point where the amount of vascular destruction precludes the use of pulmonary vasodilator therapy.[15,16] However, DLCO is a well-established prognostic marker in patients with COPD and other lung diseases and an alternate explanation is that the low DLCO patients were a high-risk group for mortality unrelated to drug administration.[17,18] The former explanation might be more plausible given that there were no deaths in the placebo group with DLCOs below this threshold. On the other hand, the disparate terminal courses of the patients who succumbed might be supportive of the latter explanation.

There are several limitations to this post hoc analysis. First, these were not prespecified analyses and were conceived only after the study was halted with the purpose of exploring potential confounding factors that impacted the study outcome. Therefore, none of these analyses and observations should be taken as conclusive but rather as hypothesis-generating, especially given that our interpretations were based on a small number of patients through pattern recognition rather than any formal statistical analyses. Our analyses of baseline haemodynamics should also be viewed with caution since the tracings were not centrally adjudicated, and patients could qualify with any right heart catheterization performed within 12 months of study entry. Therefore, the haemodynamics analyzed might not accurately reflect patients' true baseline status. It should be borne in mind that our analyses were derived from a select group of COPD patients and our findings might not be applicable to broader groups of COPD patients. Also, our observations from the treatment arm might not be seen with other potential therapies. Lastly, we do not know if any of our observations would be applicable to PH-COPD patients who did not meet the study inclusion criteria; for example, those with an mPAP <30 mmHg and/or PVR < 4 WU. Lastly, our threshold defining a potential response should not be inferred that there are PH-COPD patients who should be treated with iTRE, especially considering that the "response" rate was similar in the placebo arm. We also do not know that those patients who died after iTRE withdrawal were not destined to succumb either way. Our definitions of "adverse responders" and "potential responders" are somewhat arbitrary and require further validation and refinement. It should be noted that not all patients had evaluable data at the end of the RCT to be regarded as "responders," so our denominator of 66 might be an underestimate. Furthermore, not all patients entered the OLE, which might also have impacted our estimate of "responders" by drug withdrawal.

In conclusion, this post hoc analysis provides evidence for certain haemodynamic and lung function thresholds that can hopefully inform the design of future clinical trials in PH-COPD. It would appear that those patients with DLCO < 25% have a reduced likelihood of benefit and might be at greater risk of mortality from PH therapy, while those PH-COPD patients with FEV1 > 40% predicted and mPAP >40 mmHg appear most likely to demonstrate benefit. However, an important caveat to these thresholds for enrollment is that they will limit the number of eligible patients for clinical trial enrollment and impact the feasibility of executing the next "perfect" study. An alternate strategy to satisfy this dire unmet medical need is to allow select PH-COPD patients into future Group 1 clinical trials.

AUTHOR CONTRIBUTIONS

Steven D. Nathan wrote the first draft of the manuscript. Victoria Lacasse and Michael Di Marino analyzed the data and generated the figures and table. Steven D. Nathan, Aaron Waxman, Todd Bull, Victor Tapson, Heidi Bell, and Prakash Sista contributed ideas for analyses. All authors provided input and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

Steven D. Nathan, Aaron Waxman, Todd Bull and Victor Tapson are paid consultants for Lung Biotechnology and United Therapeutics. Victoria Lacasse, Heidi Bell, Prakash Sista, and Michael Di Marino are employees of United Therapeutics/Lung Biotechnology, the PERFECT study sponsor.

DATA AVAILABILITY STATEMENT

Data are available on request from the Sponsor, United Therapeutics Inc.

ETHICS STATEMENT

The study protocol was approved by the institutional review board at the respective participating sites and allowed for post hoc analyses.

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