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Lessons from the BEAT Trial: Implications for Inhaled Treprostinil

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Abstract

Background

Combination therapy is recommended for pulmonary arterial hypertension (PAH), part of which generally includes prostanoids, which affect both the vascular tone and vessel remodeling seen in PAH. This study tested whether a dual prostacyclin treatment strategy (oral esuberaprost + inhaled treprostinil and oral background PAH therapies) would provide additional clinical benefit.

Methods

271 World Health Organization functional class (FC) III/IV patients with PAH received placebo or 28.4 µg oral esuberaprost 4 times daily, in addition to newly initiated or ongoing inhaled treprostinil and background therapies.

Results

There was no difference between treatment groups in time to clinical worsening (primary endpoint); 49 (36.0%) patients on esuberaprost and 51 (37.8%) on placebo had a clinical worsening event. No favorable esuberaprost treatment effects were observed for the secondary or exploratory endpoints (6-minute walk distance [6MWD], Borg dyspnea score, and N-terminal pro-brain natriuretic peptide [NT-proBNP]). There were 21 all-cause deaths (esuberaprost: 8 [5.9%]; placebo: 13 [9.6%]). Post hoc exploratory analyses to investigate the effect of inhaled treprostinil on treprostinil-naïve patients (n = 151) found that the addition of inhaled treprostinil resulted in improvements in multiple components of risk status, NT-proBNP, and 6MWD from screening through week 52, irrespective of background therapy. Notably, these improvements were also seen in patients on dual background therapy.

Conclusion

While the study did not meet its primary endpoint, it suggested that monitoring patients based on proven risk scores may be highly beneficial.

Trial Registration:

Beraprost-314d Added-on to Tyvaso® (BEAT) NCT01908699; Registered 2013-07-26

INTRODUCTION

Despite treatment advances, pulmonary arterial hypertension (PAH) remains a severe disease with approximately 15% first-year mortality [1–3]. Current treatment recommendations for World Health Organization (WHO) functional class (FC) IV or persistent FC III patients with PAH include upfront or sequential combinations of phosphodiesterase-5 inhibitors (PDE5i), soluble guanylate cyclase stimulators, and/or endothelin receptor antagonists (ERA) with prostanoids, and, more recently, activin signaling inhibitors [1, 4]. Parenteral prostanoids are recommended for severe PAH, rapid progression, and poor prognosis [2, 5, 6], but their risks and administration challenges have driven development of inhaled and oral alternatives [7, 8].

Beraprost is an oral prostacyclin analogue that showed promise in patients with PAH who had improvements in hemodynamics, 6-minute walk distance (6MWD), and mortality [9–11]. Larger, controlled clinical trials in WHO FC II/III PAH demonstrated modest, potentially unsustained improvements in 6MWD [12, 13]. Esuberaprost (beraprost isomer 314d) exhibited 5-fold activity compared to the beraprost racemic mixture in vitro [14]. Initial trends in slower disease progression and improved 6MWD with beraprost [9–11, 13] suggested that a more potent isomer may result in greater treatment effects.

The BEraprost-314d Added to Tyvaso (BEAT) study evaluated whether a dual-prostanoid approach of oral esuberaprost added to inhaled treprostinil (Tyvaso®; United Therapeutics Corporation, Research Triangle Park, NC) would improve clinical outcomes over inhaled treprostinil alone. Inhaled treprostinil is characterized by rapid absorption (0.12–0.25 hours) and a relatively short half-life (4 hours) [15, 16], whereas oral esuberaprost demonstrates slower absorption (3.3 hours), lower peak plasma concentration (184.3 pg/mL), and a more protracted elimination from circulation (13.6 hours) [17–19]. It was thus hypothesized and evaluated in this study if the dual-prostanoid combination of oral esuberaprost and inhaled treprostinil would approximate the drug exposure observed with parenteral prostanoid therapy while providing a less invasive and more tolerable dual prostacyclin treatment strategy. This approach was also intended to capture the range of pharmacologic effects associated with prostacyclin analogs, including vasodilation, inhibition of platelet aggregation, and antiproliferative activity [20, 21].

METHODS

Study Design

BEAT (NCT01908699) was a phase 3, multicenter, double-blind, randomized, placebo-controlled, event-driven study designed to assess the efficacy and safety of oral esuberaprost when added to inhaled treprostinil and other background PAH therapy. The study randomized and dosed a total of 271 patients and was conducted at 77 sites in the United States and Israel. The study design was based on the hypothesis that enrichment of a population with WHO FC III/IV PAH would lead to a higher event rate.

The initial power calculation was based on an expected clinical worsening event rate of 45% after 1 year of inhaled treprostinil, which would be potentially decreased to 25% per year by the addition of oral esuberaprost. From proportional hazards over time, 113 events (approximately 240 patients) were expected to be needed to detect treatment difference at a power of 90% over a period of 1.5 years and a total follow-up time of 2.5 years. Sample size calculations were performed with nQuery Advisor 7.0 (Statsols, Cork, Ireland) using sample size methods for the log-rank statistic [22]. Due to a lower-than-expected clinical worsening event accrual rate in the study after 4 years, a re-computation of the anticipated power revealed that the power calculation exceeded 80% at 93 clinical worsening events. Therefore, the study was deemed complete and unblinded when 100 patients had clinical worsening events. All patients were given the opportunity to enroll in a long-term open-label extension study of oral esuberaprost (NCT03657095) following study completion.

Patients

Signed informed consent was obtained from each patient prior to enrollment. The study protocol and all related documents were reviewed and approved by the Institutional Review Board or Independent Ethics Committee applicable to each site. Reviews and approvals were conducted in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56) and the International Conference on Harmonisation E6 Good Clinical Practice guidance and in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki.

Female and male patients 18–80 years of age with PAH of specific etiologies were eligible for participation (**Table S1**). Patients could be receiving ≤ 2 US Food and Drug Administration-approved non-prostanoid background therapies, if the regimen was stable for ≥ 30 days before baseline. Additional inclusion criteria were the ability to walk unassisted, a 6MWD of ≥ 100 m, and right heart catheterization within 5 years showing mean pulmonary artery pressure of ≥ 25 mm Hg at rest, pulmonary capillary wedge pressure of ≤ 15 mm Hg, and pulmonary vascular resistance > 3 Wood units. Patients were required to be WHO FC III or IV with an inadequate clinical response to current therapy. Key exclusion criteria were significant left heart disease on echocardiography, pregnancy or lactation, prior exposure to beraprost or esuberaprost, PAH due to any cause not listed in the inclusion criteria, active hemorrhagic conditions, and musculoskeletal disorders that limited ambulation.

Eligible patients were randomized 1:1 to esuberaprost or placebo given orally four times daily (QID) in conjunction with inhaled treprostinil dosing. Randomization was stratified by prior naïve vs experienced inhaled treprostinil use. Experienced inhaled treprostinil patients were eligible for randomization if they had ≥ 90 days of uninterrupted inhaled treprostinil treatment with ≥ 30 days at a stable dose. Naïve patients, defined as those not taking inhaled treprostinil, entered a 90-day run-in period of inhaled treprostinil use to ensure tolerability. WHO FC was reassessed at the end of the 90-day period (baseline) and any patient achieving FC II or lower was excluded from the study prior to being randomized.

Dosing

Naïve patients were provided with inhaled treprostinil via an ultrasonic, pulsed delivery device (Tyvaso Inhalation System; United Therapeutics Corporation, Research Triangle Park, NC) and training in accordance with standard procedures. Patients naïve to inhaled treprostinil initiated inhaled treprostinil at 3 breaths (18 µg/inhalation) QID using the inhaled treprostinil ultrasonic nebulizer. If tolerated, dosing was increased over the first 2 weeks to reach a maximum target of 9 breaths (54 µg) QID, after which the inhaled treprostinil dose was kept stable or adjusted per protocol. At baseline, eligible patients were randomized to receive esuberaprost 14.2 µg or placebo taken simultaneously with inhaled treprostinil and titrated to 28.4 µg QID over the protocol-specified period. Patients unable to tolerate 28.4 µg QID remained on 14.2 µg QID, with optional re-challenge at weeks 4 or 8. Study assessments occurred at weeks 4, 8, and 12 and quarterly thereafter, with interim contacts to monitor safety, clinical worsening, and adverse events.

Primary Endpoint

The primary endpoint was the time from randomization to the first occurrence of any one of the following clinical worsening events: death (all-cause), hospitalization due to worsening PAH or related conditions, initiation of a parenteral prostanoid, disease progression, or an unsatisfactory long-term clinical response defined as ≥ 15% decrease in 6MWD from baseline and sustained WHO FC III/IV for ≥ 24 weeks. Investigators made initial assessments of suspected clinical worsening events with final determinations made by an independent endpoint adjudication committee.

Secondary Endpoints

Secondary endpoints were time from randomization to clinical failure, including clinical worsening and need for additional treatment due to lack of improvement in FC, 6MWD, Borg dyspnea score, and N-terminal pro-brain natriuretic peptide (NT-proBNP). At each visit, 6MWD, Borg dyspnea score, FC, and NT-proBNP were assessed. Exercise capacity (6MWD and Borg dyspnea score) was measured 3–6 hours after study drug administration.

Safety Assessments

Safety assessments included monitoring for treatment-emergent adverse events, vital signs, cardiac function, and concomitant medications.

Post Hoc Analyses of Inhaled Treprostinil

Post hoc assessments were conducted to evaluate the efficacy of inhaled treprostinil in patients who were naïve at study entry and initiated treprostinil as part of trial participation. Efficacy was evaluated using mean changes in NT-proBNP levels, 6MWD, WHO FC, REVEAL 2.0 risk scores [23], and COMPERA 2.0

from screening through baseline and week 52. Risk stratification used the REVEAL 2.0 calculator and the French noninvasive method [24]; available parameters included etiology, age, sex, renal insufficiency, WHO FC, heart rate, systolic blood pressure, 6MWD, and NT-proBNP. Exploratory analyses further examined the impact of background PAH therapies on treatment outcomes in this cohort of treprostinil-treated patients. These post hoc analyses were not prespecified and are considered hypothesis-generating.

Statistical Analyses

Treatment groups were compared for all measures of efficacy and safety (primary, secondary, and exploratory endpoints). Post-randomization analysis endpoints used observed case data without imputation for dropout or clinical worsening. All planned statistical analyses included the stratification variable (naïve vs experienced inhaled treprostinil) as a covariate, and post hoc exploratory analyses were stratified by background PAH therapy. Analyses of time to clinical worsening data were based on the stratified log-rank test for differences of survival/event curves with Cox proportional hazard modeling to estimate the hazard ratio and its associated 95% confidence interval. Secondary endpoints were analyzed following a pre-defined hypothesis testing strategy. Subgroup, sensitivity, and exploratory analyses were also conducted. Safety assessments for the extent of exposure and adverse events were tabulated descriptively. All analyses included any patient randomized and treated during the study.

RESULTS

Demographics

A total of 271 patients with WHO FC III/IV PAH were randomized (136 esuberaprost/135 placebo) and received study drug (Fig. 1 and **Table S1**). Most patients (89.3%) were on single or dual oral background PAH therapy. Overall, 62 esuberaprost patients (45.6%) and 58 placebo patients (43.0%) completed the study without clinical worsening or early discontinuation. The minimum duration of treatment was 16 days, and the maximum was 64.3 months. Patients were generally balanced across all subgroups.

Primary Endpoint

The primary outcome assessments for esuberaprost did not reveal a significant difference from those receiving placebo (Table 1). Clinical worsening occurred at similar rates in the esuberaprost and placebo groups (36.0% vs 37.8%). Extrapolating out to 5 years, the time to clinical worsening was not significantly different between esuberaprost and placebo (Fig. 2). Fifty-percent event-free survival probability was also similar, occurring at approximately 3 years post-randomization for both groups. The treatment groups did not show a difference for the primary endpoint of time to clinical worsening (P = 0.6), with a hazard ratio for the esuberaprost group of 0.9 (95% confidence interval, 0.6–1.3).

Table 1
First Adjudicated Clinical Worsening Events

First Adjudicated Clinical Worsening Event*, n(%)	**Overall (N = 271)**	**Placebo (N = 135)**	**Esuberaprost (N = 136)**
Total number of patients with CWEs	100 (36.9)	51 (37.8)	49 (36.0)
Death (all causes)	21 (7.7)	13 (9.6)	8 (5.9)
Hospitalization due to worsening PAH	37 (13.7)	14 (10.4)	23 (16.9)
Non-elective due to conditions related to PAH and/or right heart failure	35 (12.9)	13 (9.6)	22 (16.2)
Lung or heart/lung transplantation	2 (0.7)	1 (0.7)	1 (0.7)
Initiation of a parenteral prostanoid	20 (7.4)	13 (9.6)	7 (5.1)
Disease progression	10 (3.7)	4 (3.0)	6 (4.4)
Unsatisfactory long-term clinical response	12 (4.4)	7 (5.2)	5 (3.7)
*Confirmed by the endpoint adjudication committee. §Percentages calculated from the number of patients in a group.			
CWE, clinical worsening event; PAH, pulmonary arterial hypertension.			

Secondary Endpoints

None of the secondary objectives evaluated (overall mortality, change from baseline at each clinical visit for 6MWD, FC, Borg dyspnoea score, and NT-proBNP) demonstrated a treatment effect favoring esuberaprost (P > 0.05 for all parameters). Subgroup analysis did not identify any factors favoring a treatment effect for esuberaprost (Fig. 3).

Esuberaprost was well tolerated when added to inhaled treprostinil and showed no additional safety signals compared with placebo (**Table S2**).

Post Hoc Analyses of Inhaled Treprostinil

The exploratory post hoc analyses included 151 patients who were naïve to inhaled treprostinil at the start of the study, remained eligible for enrollment after 90 days of treatment, and were subsequently stratified by background therapy (Table 2). The majority of patients were on dual background therapy (50.3%) and 69.7% were female. After the 90-day run-in period with inhaled treprostinil, patients achieved approximately 4.29 breaths per session (**Table S4**).

Table 2
Demographic Characteristics of Treprostinil-Naïve Patients at Screening

Characteristic	**Background Therapy**		
	None	**Single**	**Dual**
	(n = 24)	**(n = 51)**	**(n = 76)**
Age, years, mean (SD)	60 (14.6)	59 (13.3)	54 (13.6)
Female, n (%)	15 (63%)	38 (75%)	54 (71%)
Caucasian, n (%)	21 (100%)	43 (100%)	65 (100%)
BMI, mean (SD)	29.2 (6.9)	29 (5.6)	30 (7.2)
Region, n (%)			
Israel	6 (25)	9 (18)	7 (9)
United States	18 (75)	42 (82)	69 (91)
Time since diagnosis, years, mean (SD)	0.2 (0.2)	2.9 (5.0)	3 (3.0)
Etiology of PAH, n (%)			
Idiopathic	15 (63)	32 (63)	39 (51)
Collagen vascular disease	9 (38)	15 (30)	28 (37)
6MWD, meters, mean (SD)	281 (148)	313 (102)	354 (97)
Modified Borg Score, mean (SD)	4.4 (2.0)	4.7 (2.4)	3.9 (2.1)
WHO functional class, n (%)			
III	21 (88)	46 (90)	72 (95)
IV	3 (13)	5 (10)	4 (5)
REVEAL 2.0 risk category at screening*	Naïve cohort (%)	Experienced cohort (%)	
Low risk	18.1	37.6	
High risk	48.7	38.5	

Characteristics determined at time of screening or baseline for BEAT patients based on interview and medical history. 6MWD, modified Borg score, and WHO FC were assessed at baseline.

6MWD, 6-minute walking distance; BMI, body mass index; ERA, endothelin receptor antagonists; FC, functional class; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitors; SD, standard deviation; sGC, soluble guanylate cyclase; WHO, World Health Organization.

Among treatment-naïve patients, REVEAL 2.0 risk scores showed a reduction in high-risk classification from screening (45.0%) to baseline after initiation of inhaled treprostinil (35.1%) and further to week 52 (22.4%; Table 3). In contrast, the proportion of patients in the low-risk category increased over the same period. Comparable results were seen with WHO FC and COMPERA 2.0 risk scores (Table 3).

Table 3
Post Hoc Risk Assessment Scores for Treprostinil-Naïve Patients: Screening, Baseline, and Week 52

Risk Score, n (%)	Background Therapy											
	None			Single			Dual			Total		
	Screening (n = 24)	Baseline (n = 24)	Week 52 (n = 17)	Screening (n = 51)	Baseline (n = 51)	Week 52 (n = 38)	Screening (n = 76)	Baseline (n = 76)	Week 52 (n = 52)	Screening (n = 151)	Baseline (n = 151)	W 5 (n 1
REVEAL 2.0												
Low	3 (12.5)	5 (20.8)	6 (35.3)	9 (17.7)	15 (29.4)	18 (47.3)	30 (39.5)	29 (38.2)	31 (59.6)	42 (27.8)	49 (32.5)	5 (5
Intermediate	5 (20.8)	9 (37.5)	5 (29.4)	17 (33.3)	14 (27.5)	11 (29)	19 (25)	26 (34.2)	12 (23.1)	41 (27.2)	49 (32.5)	2 (2
High	16 (66.7)	10 (41.7)	6 (35.3)	25 (49)	22 (43.1)	9 (23.7)	27 (35.5)	21 (27.6)	9 (17.3)	68 (45.0)	53 (35.1)	2 (2
FC												
I	—	—	1 (5.9)	—	—	3 (7.8)	—	—	5 (9.6)	—	—	9 (8
II	—	—	7 (41.2)	—	—	17 (44.8)	—	—	18 (34.6)	—	—	4 (3
III	21 (87.5)	21 (87.5)	8 (47)	46 (90.2)	46 (90.2)	17 (44.8)	72 (94.7)	74 (97.4)	29 (55.8)	139 (92.1)	141 (93.4)	5 (5
IV	3 (12.5)	3 (12.5)	1 (5.9)	5 (9.8)	5 (9.8)	1 (2.6)	4 (5.3)	2 (2.6)	—	12 (7.9)	10 (6.6)	2 (1
COMPERA 2.0												
High	6 (26.1)	3 (13.1)	2 (12.5)	5 (10)	3 (5.8)	2 (5.3)	2 (2.6)	2 (2.6)	—	13 (8.7)	8 (5.3)	4 (3
Intermediate-High	12 (52.2)	13 (56.5)	7 (43.8)	28 (56)	24 (47.1)	7 (18.4)	32 (42.1)	26 (34.2)	10 (20.8)	72 (48.3)	63 (42.0)	2 (2
Intermediate-Low	5 (21.7)	7 (30.4)	2 (12.5)	17 (34)	24 (47.1)	23 (60.5)	42 (55.3)	48 (63.2)	19 (39.6)	64 (43.0)	79 (52.7)	4 (4
Low	—	—	5 (31.2)	—	—	6 (15.8)	—	—	19 (39.6)	—	—	3 (2

Examination of the subset of patients available for post hoc REVEAL 2.0 risk calculations at screening and week 52. Scores were only calculated for patients with all variables available. Score 0–6: low-risk; score 7 or 8: intermediate risk; and score ≥ 9: high-risk.

FC, functional class; REVEAL, Registry to EValuate Early And Long-term PAH disease management.

The addition of inhaled treprostinil led to a decrease in NT-proBNP levels across all groups, a trend evident from baseline (Fig. 4A). Changes in mean 6MWD from screening were observed starting at baseline and continued through week 52, following a similar response pattern to NT-proBNP, with improvements seen in all 3 subgroups (Table 4 and Fig. 4B). At week 52, patients on dual background therapy and those with no previous background therapy exhibited comparable improvements. Additionally, at week 52, treprostinil-naïve patients demonstrated significant reductions in REVEAL 2.0 risk scores across all background therapy groups (Table 5). Additional subgroup data may be found in the supplemental tables.

Table 4
Mean 6MWD for Treprostinil-Naïve Patients

Background Therapy	Timepoint	N	6MWD, mean (SD)	Change from Screening, mean (SD)	P value
None	Screening	24	280.6 (148.4)	—	—
	Baseline	24	312.2 (149.1)	31.6 (83.5)	0.077
	Week 52	16	318.7 (186.4)	40.1 (95.7)	0.115
Single	Screening	51	313.2 (102.2)	—	—
	Baseline	51	327.8 (86.8)	14.6 (49.5)	0.041
	Week 52	38	337.6 (104.0)	27.9 (72.3)	0.023
Dual	Screening	76	354.3 (97.3)	—	—
	Baseline	76	373.7 (102.5)	19.4 (51.3)	0.002
	Week 52	48	409.4 (108.2)	41.5 (65.8)	< 0.0001
Note: P-value is obtained from t test.					
6MWD, 6-minute walk distance.					

Table 5
Mean REVEAL 2.0 Risk Score for Treprostinil-Naïve Patients

Background Therapy	Timepoint	N	REVEAL 2.0, mean (SD)	Change from Screening, mean (SD)	P value
None	Screening	23	8.9 (2.8)	—	—
	Baseline	23	7.8 (2.5)	−1.3 (1.7)	0.002
	Week 52	16	7.4 (3.2)	−1.8 (2.7)	0.016
Single	Screening	50	7.8 (2.5)	—	—
	Baseline	51	7.5 (2.5)	−0.4 (1.5)	0.104
	Week 52	38	6.7 (2.5)	−1.2 (2.1)	0.001
Dual	Screening	76	7.2 (2.4)	—	—
	Baseline	75	6.9 (2.4)	−0.3 (1.6)	0.078
	Week 52	47	5.7 (2.7)	−1.5 (2.1)	< 0.0001
Note: P-value is obtained from t test.					
REVEAL, US Registry to EValuate Early And Long-term PAH disease management; SD, standard deviation.					

DISCUSSION

The BEAT trial enrolled patients with WHO FC III/IV PAH who had unsatisfactory or declining response to therapy to assess whether combined oral and inhaled prostanoid treatment could delay clinical worsening vs single prostanoid therapy. Esuberaprost and inhaled treprostinil have distinct pharmacological profiles, with esuberaprost having a slower absorption (3.3 hours vs 0.12–0.25 hours, respectively), lower peak plasma concentration (184.3 pg/mL vs 0.91–1.32 ng/mL), and a more prolonged elimination compared with the rapid absorption and shorter half-life of inhaled treprostinil (13.6 hours vs 4 hours) [15–19]. Although the dual-prostanoid regimen was well tolerated, it did not improve time to clinical worsening or secondary endpoints compared with inhaled treprostinil and background therapy.

Although the negative results in this study are disappointing, it is worthwhile highlighting observations that can be instructive and may better inform future trials, while also leveraging this unique opportunity to analyze the impact of initiating inhaled treprostinil in patients already receiving dual background therapy. Current guidelines for PAH treatment recommend upfront therapy with an ERA and PDE5i [1, 25], but do not provide specific recommendations for inhaled treprostinil in combination with dual background therapy. Studies evaluating REVEAL risk scores found that a majority of newly diagnosed patients do not achieve low-risk status at 6 months or at 2 years using dual ERA and PDE5i [26, 27]. Triple drug therapy is currently recommended for intermediate and high-risk patients at 3–6 months if initial treatment is not effective [1, 4]. Upfront triple-combination therapy with the inclusion of a parenteral prostanoid has also shown promise in small cohorts of severely ill patients with PAH, improving right heart function, WHO FC, exercise capacity, and lowering REVEAL risk scores [28, 29].

The exploratory post hoc analyses completed here, which stratified treprostinil-naïve patients by background therapy, demonstrated improvements in multiple components of risk status and individual clinical variables, regardless of background therapy. Notably, improvements were observed in patients who were on dual therapy. These observations are consistent with previous studies that showed significant improvement in hemodynamics, exercise capacity, and symptoms with inhaled treprostinil, where the majority of patients were on ≥ 1 background therapy [7, 30]. Without a placebo control, all conclusions regarding this effect must be understood with caution.

Nevertheless, comparison with the 12-week TRIUMPH study and its long-term extension provides supportive context for these post hoc observations. TRIUMPH randomized patients with PAH on a stable dose of bosentan or sildenafil to receive either inhaled treprostinil or placebo QID [7], and demonstrated a placebo-corrected median 6MWD improvement of 20 m at 12 weeks, with greater benefit in those receiving bosentan vs sildenafil. In the open-label extension, median within-group improvements reached 32 m after 18 months [31]. In BEAT, mean 6MWD improvements over 52 weeks were similar or greater across all background therapy strata, including dual therapy. Although direct comparison is limited by differences in study design and analyses, the TRIUMPH findings lend plausibility to the durability and breadth of benefit observed in this post hoc analysis.

It is important to note that the exploratory post hoc analyses were not pre-planned, and thus, are subject to inherent limitations. Additionally, the study was not originally powered for these analyses, and the findings should be interpreted as hypothesis-generating rather than confirmatory.

In conclusion, esuberaprost added to inhaled treprostinil in patients with PAH classified as WHO FC III/IV and who are already on single or dual oral therapies did not delay clinical worsening. The analysis of the placebo group also suggested sustained efficacy of inhaled treprostinil on single and dual background therapy. Our results provide enlightening observations for future trials: screening patients based on risk scores may be more beneficial than determination based on a single factor, such as WHO FC, and a drug class may have a maximum discernable treatment effect that may not be enhanced with complementary drugs within the same class.

Abbreviations

6MWD 6-minute walk distance

BEAT Beraprost-314d Added-on to Tyvaso

BMI Body mass index

CI Confidence interval

CVD Cardiovascular disease

CWE Clinical worsening event

ERA Endothelin receptor antagonist

FC Functional class

HIV Human immunodeficiency virus

ISR Israel

NT-proBNP N-terminal pro-brain natriuretic peptide

PAH Pulmonary arterial hypertension

PDE5i Phosphodiesterase-5 inhibitor

QID Four times daily

REVEAL Registry to Evaluate Early and Long-term PAH Disease Management

SD standard deviation

sGC Soluble guanylate cyclase

TRIUMPH TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension

WHO World Health Organization

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by Western IRB (IRB00000533) institutional review board and at independent institutional review boards at respective participating sites, as required by each site, and allowed for post hoc analyses. All participants provided written informed consent prior to enrollment.

CONSENT FOR PUBLICATION

Not applicable.

Competing Interests

MK and BM have nothing to disclose. SB has received grants from United Therapeutics and Gossamer Bio, and consultancy fees from Merck and Janssen. RCB has received research support from Abbott Industries. RS has received consulting fees and honoraria from United Therapeutics and Merck. HJF has received grants, contracts, or consulting fees from Merck, Gosammer Bio, Cereno, United Therapeutics, Pfizer, Jannsen, and Liquidia.JS has received consulting fees from Johnson and Johnson, Merck, Liquidia, and Bayer; and participated as a member of a PHA PHCC review committee. SMS has received grants from Reata Pharmaceuticals, United Therapeutics, Lung RX, Gossamer, and Liquidia.ABW or their institution has received consulting fees from Aria CV, Gossamer Bio, Merck, Tektonics, United Therapeutics, Pulmovant, and OrphAI; and payment from Insmed for participation in Data Safety Monitoring Board or Advisory Board. DI has received honoraria payments from Bayer. RJO has received grants, consulting fees, and meeting support from United Therapeutics. JS, PS, MD, AS, MT, ML, YR, MB, and FR are employees of and may have received stock or stock options from United Therapeutics. RN has received consulting fees and honoraria from AOP Orphan; payment or honoraria from Lung Biotechnology, United Therapeutics, and Johnson & Johnson; support for meeting attendance from AOP Orphan and United Therapeutics; and payments for participating in a Data Safety Monitoring Board or Advisory Board with AOP Orphan and United Therapeutics.

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Author Contribution

MRK, SB, RS, RCB, HJF, BM, JSS, SMS, ABW, DI were responsible for the Investigation, reviewing data and editing manuscript; RJO and RN contributed to conceptualization, reviewing data and writing/editing manuscript; JS, PS, MIL, MED, MLT, AS contributed to data curation, project administration, supervision of study conduct and reviewing/editing manuscript; YR, MB, FR contributed to post hoc analyses and reviewing/editing manuscript.

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Data Availability

Data are available upon reasonable request. Interested researchers will be able to submit a research proposal via www.utcrequests.com. Proposals will be evaluated by the sponsor. Once research proposal has been approved and data sharing agreement signed between sponsor and investigator.

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Figures

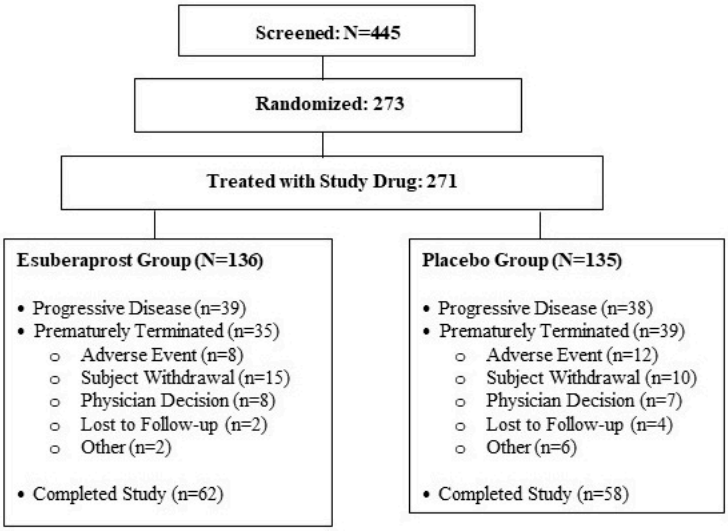


Figure 1

Summary of Patient Disposition

A total of 273 patients were randomized and of those, 271 received treatment: 136 patients in the esuberaprost group and 135 in the placebo group. Of the 271 patients that received treatment, 62 (45.6%) patients in the esuberaprost group and 58 (43.0%) patients in the placebo group completed the study without clinical worsening or early discontinuation. Early discontinuation occurred in 151 (55.7%) patients during the study with similar occurrence between treatment groups.

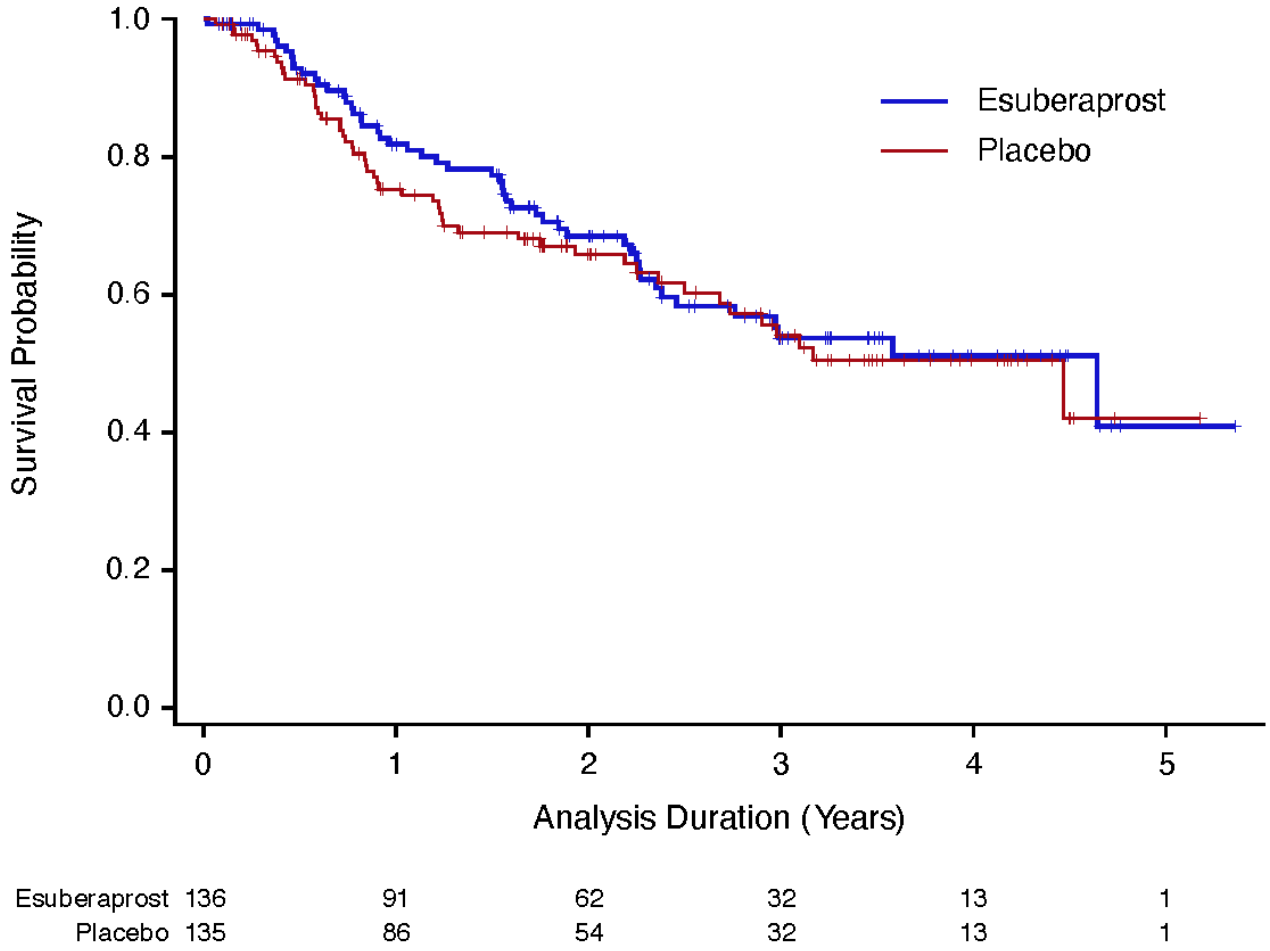


Figure 2

Kaplan Meier Plot of Time to Clinical Worsening

Plot of time to first clinical worsening event. Survival probability represents the absence of clinical worsening. Clinical worsening events were defined as death (all-cause), hospitalization due to worsening PAH or related conditions, initiation of a parenteral prostanoid, disease progression, or an unsatisfactory long-term clinical response defined as, at least 15% decrease in 6MWD from baseline and sustained WHO FC III/IV for at least 24 weeks. There was no significant difference between placebo- and esuberaprost-treated patients (*P*= 0.62), with a hazard ratio for the esuberaprost group of 0.9 (95% CI, 0.6–1.3). All patients not meeting the clinical worsening event definition by the end of the study were censored in the survival analyses.

6MWD, 6-minute walk distance; CI, confidence interval; FC, functional class; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

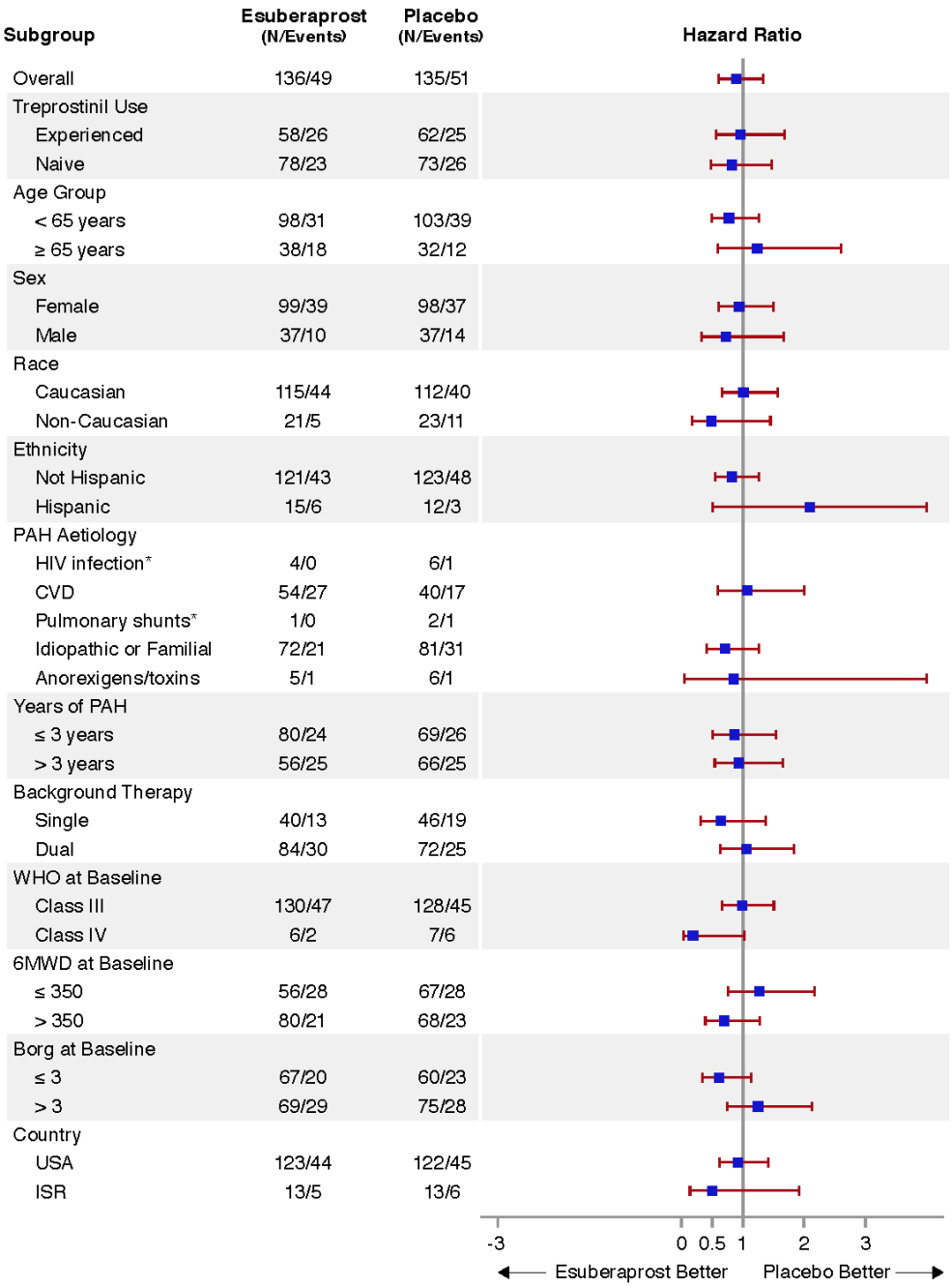


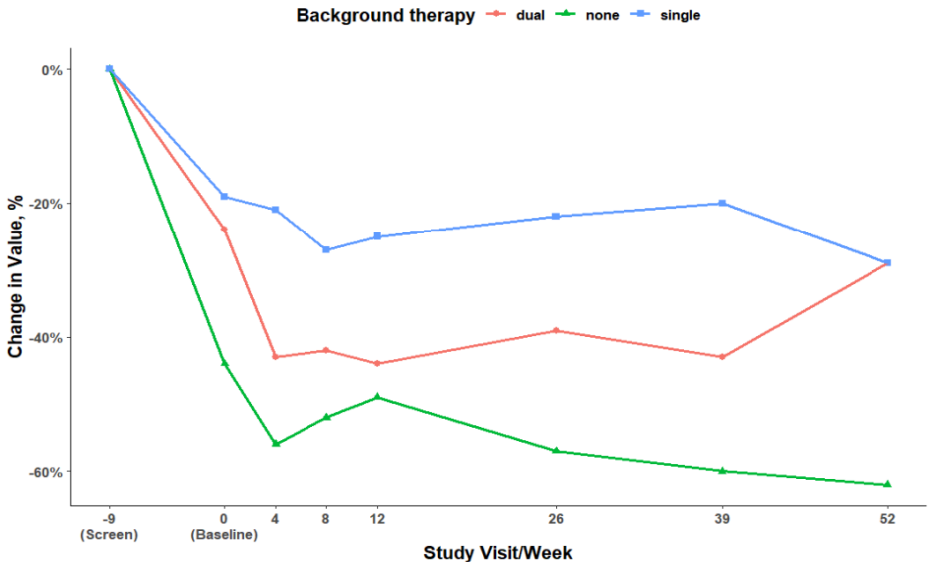
Figure 3

Forest Plot of Hazard Ratio Analysis of Subgroups

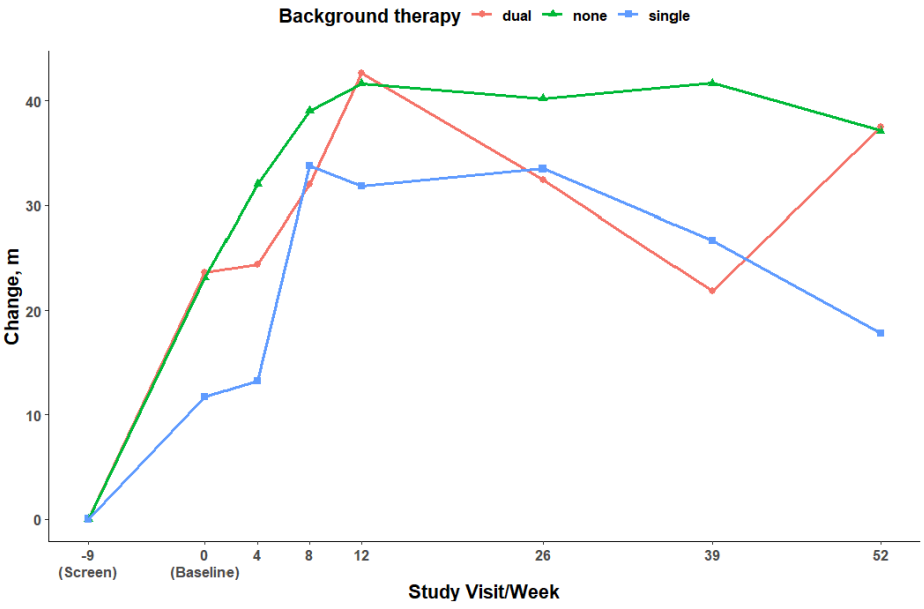
*Unable to be calculated due to small sample sizes.

All analyses were stratified for treprostinil use, except for treprostinil use subgroups. No significant treatment effect was seen for any subgroup. Boxes to the right of marker line 1 indicate a positive treatment effect for the addition of esuberaprost vs placebo. Note: HIV and shunt data are not available due to small population sizes.

6MWD: 6-minute walking distance; CVD, cardiovascular disease; FC, Functional Class; HIV, human immunodeficiency virus; ISR, Israel; PAH, pulmonary arterial hypertension; USA, United States; WHO, World Health Organization.



A



B

Figure 4

Mean Change in A) NT-proBNP and B) 6MWD for Treprostinil-Naïve Patients from Screening by Background Therapy

Mixed-effect model repeat measurement analysis.

6MWD, six-minute walk distance; NT-proBNP, N terminal pro-brain natriuretic peptide.

Supplementary Files

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