

Effect Of Esuberaprost On Morbidity And Mortality In World Health Organization (WHO) Functional Class III And IV (FC III/IV) Patients With Pulmonary Arterial Hypertension (PAH): Results From The Randomized, Double-Blind, Placebo-controlled Phase 3 Trial- Beraprost-314d Added To Tyvaso (BEAT).

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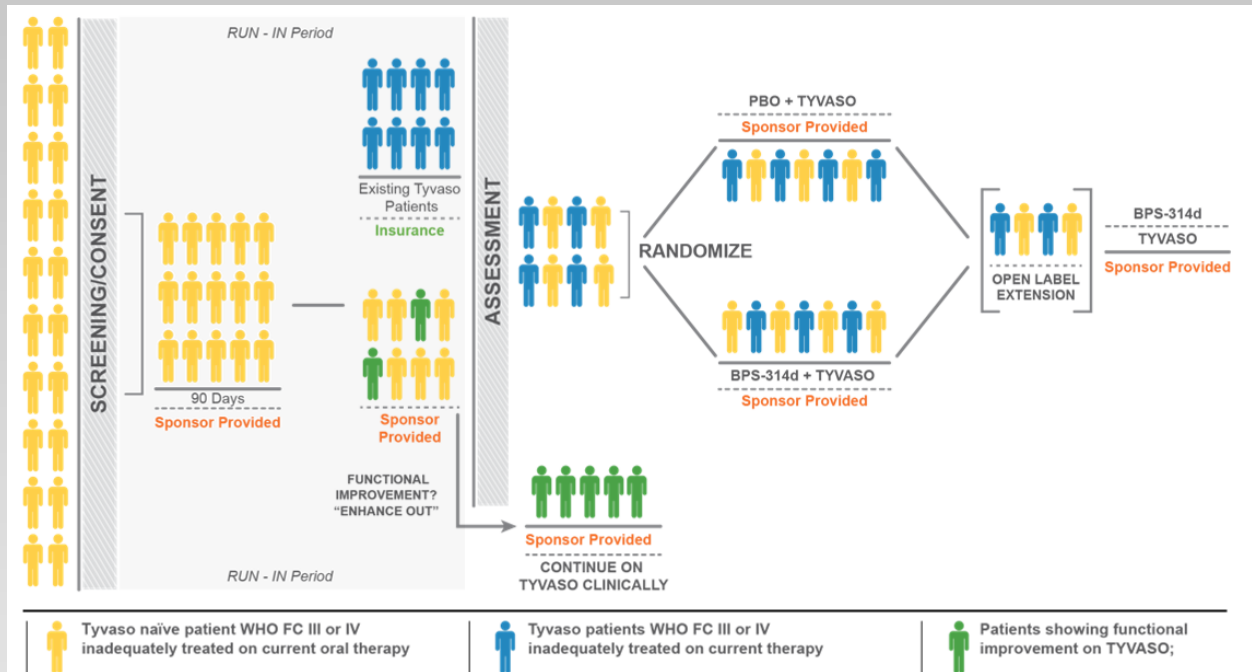
Background

The BEAT Study (BPS-314d-MR-PAH-302) was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, event-driven study designed to assess the efficacy and safety of oral esuberaprost versus placebo when added on to inhaled treprostinil in FC III-IV patients with PAH. High peak and relatively low trough prostacyclin levels can occur with oral and inhaled therapies for PAH, due to a relatively short half-life and may affect tolerability. We tested the hypothesis that a combination of two different prostanoids, a fixed dose oral esuberaprost (ESU) and inhaled treprostinil (iTRE) delivered by distinct routes would improve patient outcomes by approximating the more even prostacyclin levels of parenteral prostanoid delivery.

Methods

The BEAT study was conducted at 77 sites in the US and Israel. All subjects were WHO Functional Class III and IV PAH patients receiving background iTRE at the time of randomization to ESU or placebo (PBO) (See Fig 1). Those not experienced with iTRE at screening entered a 90-day run-in period to ensure tolerability before being randomized. Background oral PAH therapy was allowed (e.g. endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors/soluble guanylate cyclase stimulators but no other prostanoids). Eligible patients were randomized 1:1 to ESU (fixed dose of 28.4 µg orally 4 times a day) or PBO, with randomization stratified for the use of inhaled treprostinil (naïve or experienced). Subjects, study site personnel, the Sponsor, and the EAC were blinded to treatment group assignments.

Fig 1: BEAT Study Design

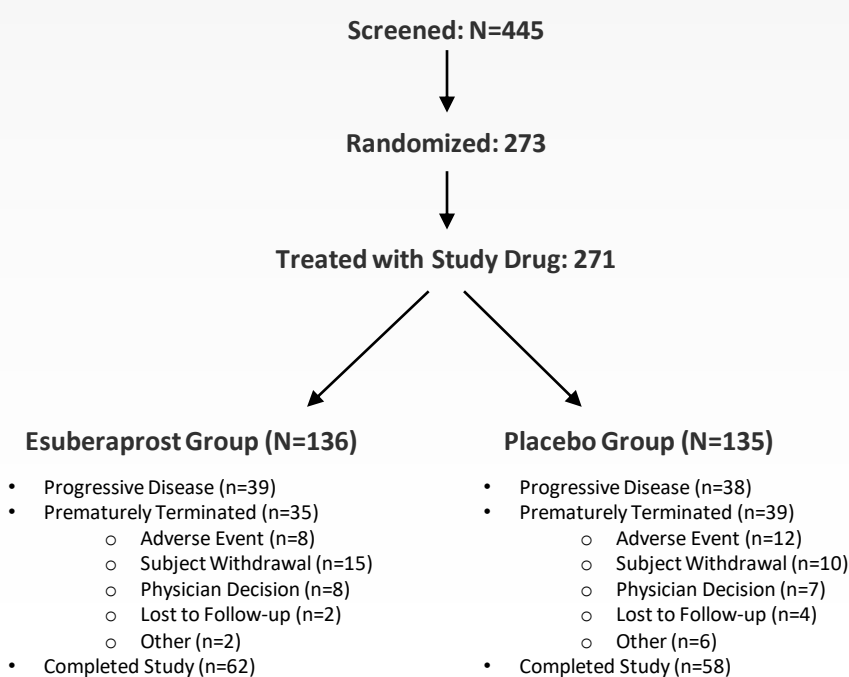


Clinical study visits occurred at Weeks 4, 8, 12 and quarterly thereafter. The primary endpoint was to compare the effects of ESU vs PBO as measured by time to clinical worsening i.e., from randomization to the 1st occurrence of any one of the following events: death (all causes), hospitalization due to worsening PAH, use of parenteral prostacyclin, disease progression, or unsatisfactory long-term clinical response. Each event was confirmed by an independent endpoint adjudication committee. Secondary endpoints included changes from baseline in: six-minute walk distance (6MWD), Modified Borg Dyspnea score, WHO Functional Class, and N-terminal pro-brain natriuretic peptide, at each clinical visit.

Results

- A total of 273 patients were randomized; 271 received study drug (136 in ESU and 135 in PBO arms, respectively) and were included in the analyses of efficacy and safety. (See Fig 2). An initial target of 113 patients with an independently adjudicated clinical worsening event (CWE) was pre-specified. However, the Sponsor deemed the study was complete after 100 patients achieved an adjudicated CWE and all subjects were rolled over into an open label study.

Fig 2: Summary of Subject Accountability and Disposition – Randomized Population



- The demographics and baseline characteristics were similar in both arms (See Table 1).

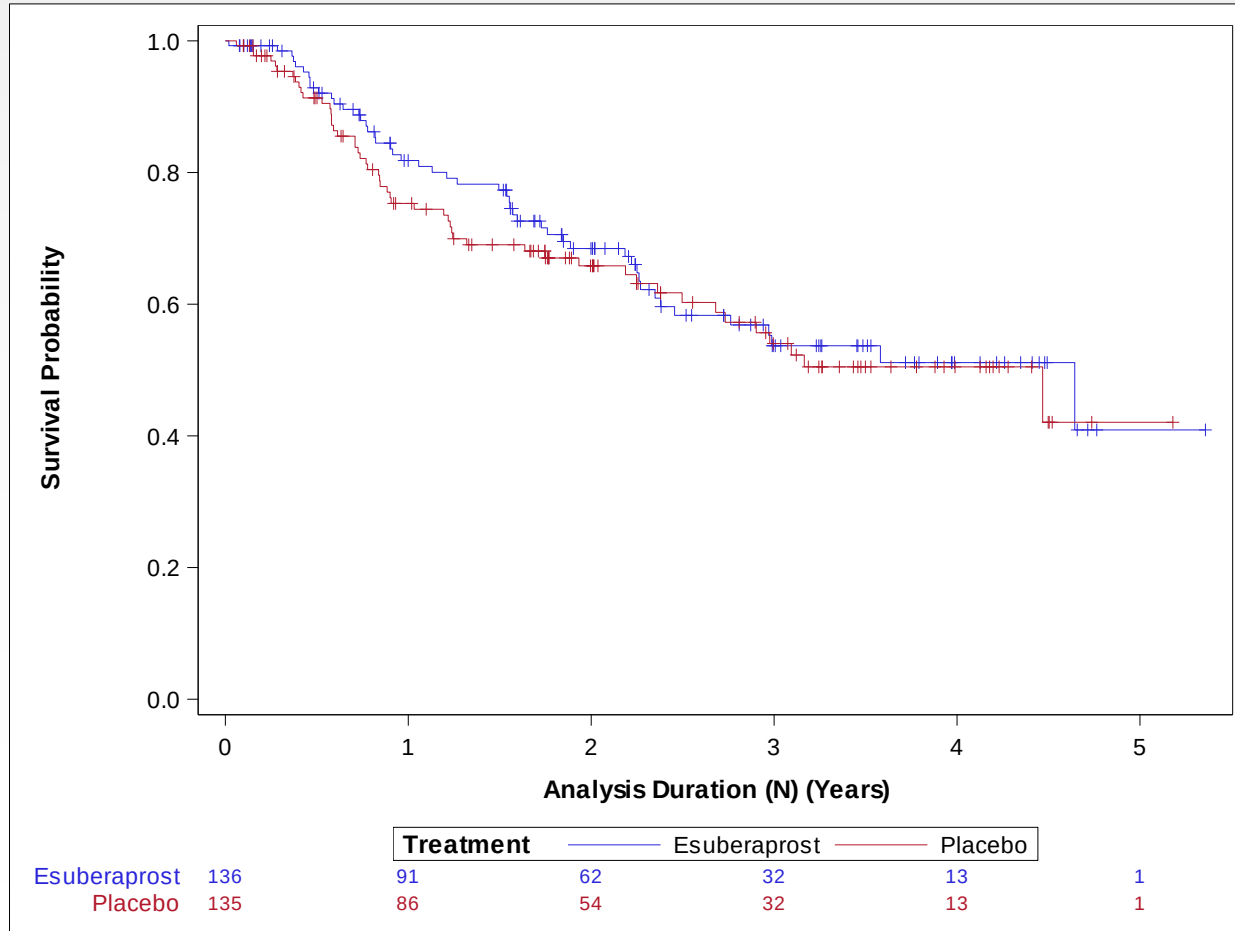
Table 1: Summary of Baseline Characteristics

	Placebo (N=135)	Esuberaprost (N=136)
Mean Age years (SD)	56 (13.3)	55 (13.6)
Female	98 (73%)	99 (73%)
Caucasian	112 (83%)	115 (85%)
Mean BMI (SD)	30 (6.6)	30 (6.6)
Patients from Israel	13 (10%)	13 (10%)
Single Background at Screening ERA PDE5i/sGC iTRE	8 (5.9%) 16 (11.9%) 4 (3%)	6 (4.4%) 21 (15.6%) 1 (0.7%)
Dual Background at Screening (Any two of ERA, PDE5i/sGC, iTRE)	58 (43%)	53 (39%)
Triple Background at Screening (ERA+PDE5i/sGC+iTRE)	36 (26.7%)	44 (32.4%)
Naïve to Tyvaso at Screening	73 (54%)	78 (57%)
Mean Years of PAH (SD)	4 (4.5)	4 (3.9)
Idiopathic/Familial	81 (60%)	72 (53%)
Mean Baseline 6MWD in meters (SD)	343 (114)	360 (107)
Mean Baseline Modified Borg Score (SD)	3.8 (2.1)	3.6 (1.9)
Baseline WHO FC IV	7 (5%)	6 (4%)

Efficacy Results-Primary

- The overall one-year event rate in this study was 19% and lower than expected for this population. The addition of ESU to iTRE (N=49/136 or 36%) was not statistically significant in comparison to iTRE alone (N=51/135 or 37.8%) for affecting the time to clinical worsening (log-rank p=0.618; Hazard Ratio 0.9 [0.6-1.3]). Kaplan Meier curve of Event Free Survival (Fig 3) did not show significant differentiation between the two arms.

Fig 3: Kaplan-Meier Plot of Time to Clinical Worsening – FAS Population



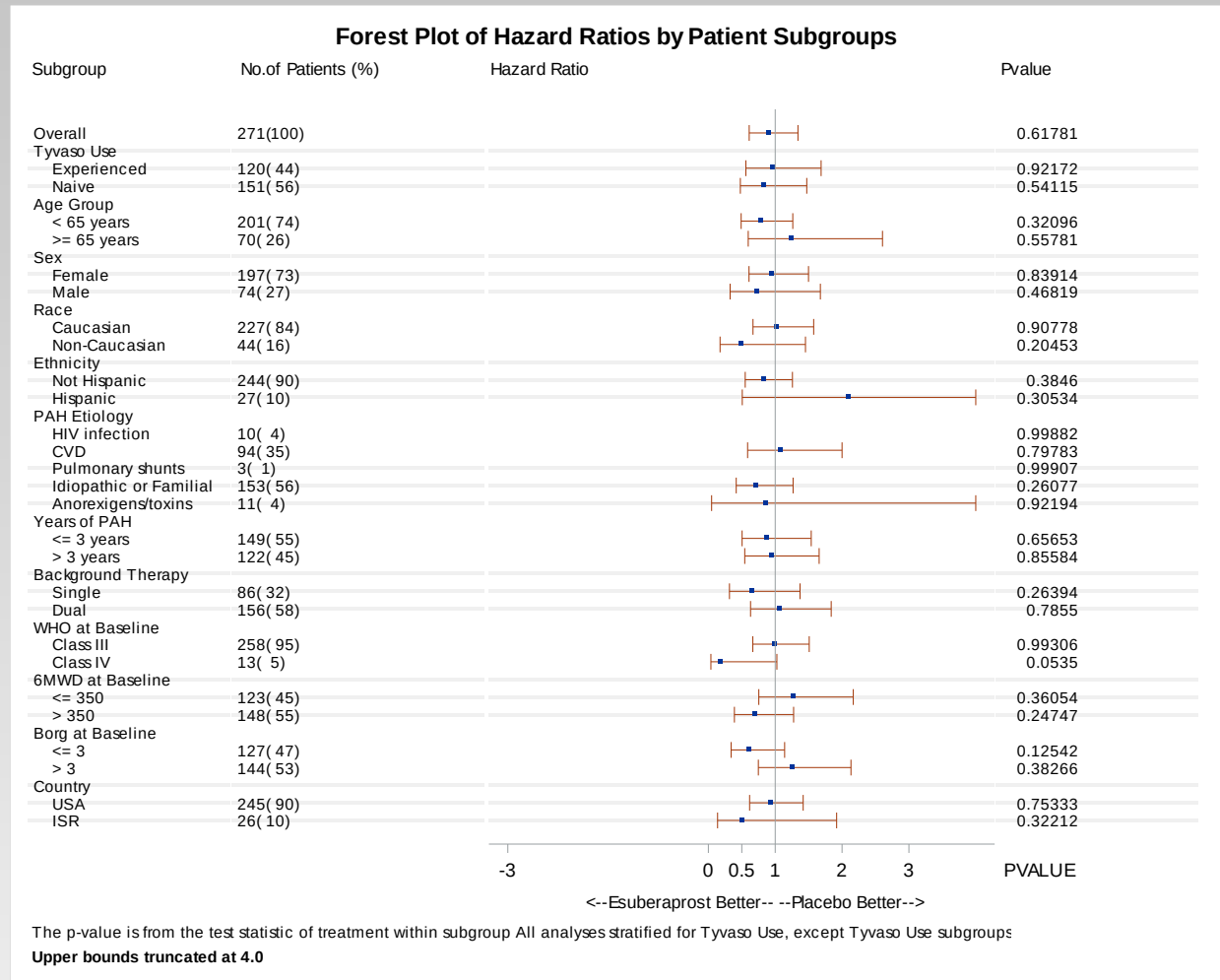
- Components of the Primary outcome showed no apparent difference between the two arms (Table 2)

Table 2: Analysis of Components of Primary Outcome

Components of Primary Outcome Contribution and Prevalence	Overall (N=271) n (%)	Placebo (N=135) n (%)	ESU (N=136) n (%)
Confirmed by Endpoint Adjudication Committee			
Total Number of Clinical Worsening Events	100	51	49
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 hospitalization caused by 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)
Atrial septostomy	0	0	0
Initiation of a parenteral prostacyclin	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)

- Subgroup analyses did not identify factors favoring a treatment effect for ESU (see Figure 4).

Fig 4: Forest Plot for all subgroup analyses



Efficacy Results-Secondary

- Overall, none of the secondary objectives evaluated (Overall mortality, change from baseline at each clinical visit for 6MWT, WHO Functional Class, Modified Borg Dyspnea score, and N-terminal pro-brain natriuretic peptide) demonstrated a treatment effect favoring ESU (p=NS for all parameters).

Safety Results

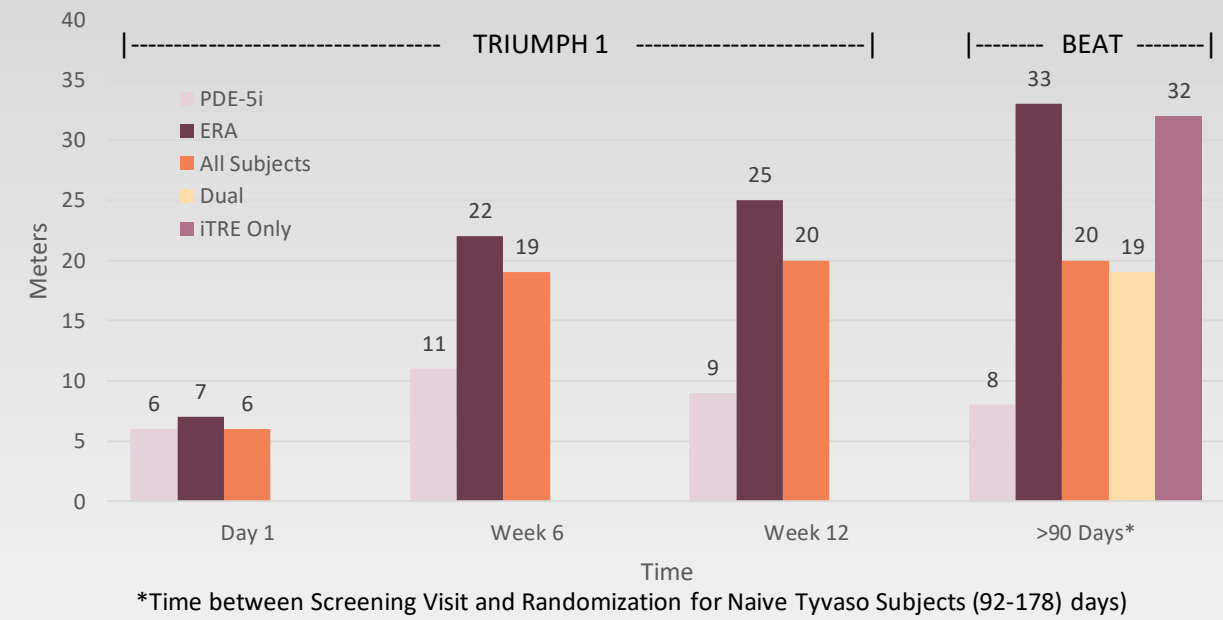
ESU was safe and well-tolerated when added to iTRE and showed no additional safety signals when compared to iTRE alone. The following observations are based on the results of the overall safety analyses. Nearly all subjects (98.5%) in either treatment group had at least 1 TEAE, with:

- 92 (67.2%) subjects in the esuberaprost group and 86 (62.4%) subjects in the placebo group who experienced at least 1 TEAE considered attributable to study drug.
- In the ESU group, the most commonly reported (>10% subjects) AEs considered attributable to study drug were nausea (18.2%); diarrhoea (14.6%); pain in jaw (10.9%); headache (35.8%); and flushing (10.9%). These events are generally known and expected pharmacological effects of esuberaprost and were observed at severities and frequencies consistent with those seen in other esuberaprost studies.
- Serious TEAEs were reported for 75 (54.7%) subjects in the esuberaprost group and 78 (58.2%) subjects in the placebo group, the events reported were expected for a population with this indication.
- Of the 172 serious TEAEs reported for the ESU group, 2 were assessed as probably related and 14 were assessed as possibly related, the remaining 156 were assessed as unlikely, unrelated, or unassessable/unclassifiable.
- There were a total of 49 deaths during this study: 27 deaths in the esuberaprost group and 22 deaths in the placebo group, which was not statistically significant.
- No clinically meaningful differences between treatment groups were observed with respect to TEAEs based on laboratory, coagulation, vital sign, or ECG abnormalities.

Discussion

- The BEAT study was the first randomized Phase 3 enrichment study to evaluate the treatment effect of the single pharmacologically active isomer ESU, as an oral fixed-dose tablet, on top of a stable regimen that included an approved prostanoid, iTRE.
- Addition of oral ESU to a background regimen including iTRE did not demonstrate a meaningful improvement in morbidity and mortality events compared to addition of placebo.
- A treatment regimen of oral background therapies with iTRE was more robust and effective than initially hypothesized:
 - Based on the literature available during the design and inception of the study in 2013 (Benza et al 2011, Voswinckel et al 2009), the one-year clinical worsening event rate for the PAH population (all FCs) was approximately 15%. We hypothesized that enrichment of a select population (FC III-IV) would lead to a higher event rate of 35-45%.
 - However, study results showed that patients treated on oral background therapies and iTRE, experienced a much lower than hypothesized mean rate of 19% at one year (ESU arm: 16%, PBO arm: 22%). Thus, the observed one-year rate of clinical worsening in the enriched population studied (FC III-IV) was similar to the general PAH population (all FCs) under effective treatment, suggesting a robust background regimen for the select population in this study.
 - Moreover, in the most recent large Phase 3 study in PAH (GRIPHON study, Sitbon 2015), the FC III-IV subset of patients exhibited an overall event rate (for study duration) of 52% (168 of 322 subjects) and 35% (103 of 256 subjects) in the placebo and selexipag arms, respectively. Similarly, the overall event rate (for study duration) in this study was 38% (51/135) and 36% (49/136) on PBO and ESU arms, respectively. This lends further credence to the possibility that all subjects received a robust background regimen that included iTRE.
- We also compared the treatment effect of iTRE among BEAT patients with those from the TRIUMPH study, to verify that the contribution of iTRE was similarly robust (see Fig 5). The 6MWD results demonstrated a similar benefit in exercise capacity as previously reported, which appeared to be durable, as inferred from the overall lower than expected event rate in our study patient population. This also appears to be consistent with the TRIUMPH OLE study, which although uncontrolled, suggested sustained durability over an 18-24-month period in 6MWD and FC (Benza 2011).
- ESU administered as a fixed dose (28.4 µg QID) failed to provide an additional benefit on top of the effective background treatment regimen, however, given the favorable safety profile for ESU, the question remains if a 'titrated to tolerability' dose of ESU would exhibit a larger treatment effect. Nevertheless, given the better than anticipated effectiveness of the background treatment regimen observed, it is expected that a rather prohibitively large study would be needed to tease out such a treatment effect for ESU and perhaps, generally for most dual-prostanoid regimens.

Fig. 5: Comparison of Change from Baseline in 6MWD between TRIUMPH and BEAT Study patients that were naïve to Tyvaso**



**Hodges-Lehman between-treatment median values excerpted from TRIUMPH study (McLaughlin et al 2010). Mean change from baseline values are depicted for BEAT. Breakdown of background Drug Class among TRIUMPH patients: N=77 (bosentan), N=38 (PDE5i) on iTRE arm; BEAT patients (N=37 for PDE5i; N=14 for ERA; N=151 for All subjects; N=76 for Dual drugs; N=24 for no background therapy)

Conclusion

Combining the two prostanoids ESU and iTRE in WHO Class III and IV PAH patients on non-prostanoid background PAH therapy did not delay time to clinical worsening compared to iTRE alone nor did this regimen improve the secondary end points evaluated in this study.

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