Supplemental Material for: Impact of Inhaled Treprostinil on Risk Stratification with Noninvasive Parameters: A post hoc analysis of the TRIUMPH and BEAT studies

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BEAT Clinical Study Description

Study design

The BEAT study (BPS-314d-MR-PAH-302) was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, event-driven study. It was designed to assess the efficacy and safety of adding oral esuberaprost versus placebo to inhaled treprostinil treatment with or without background pulmonary arterial hypertension (PAH) therapy. The study included a total of 273 patients with PAH in World Health Organization (WHO) Functional Class (FC) III or IV.

The study was conducted from June-2013 to February-2019 at 77 sites in the US and Israel. Subjects naïve to inhaled treprostinil at screening entered a 90-day initiation period to ensure tolerability before being randomized. Eligible patients were randomized 1:1 to oral esuberaprost (target dose of 28.4 μg orally 4 times daily) or placebo. Randomization was stratified by naïve or experienced treprostinil usage at screening visit. Clinical study visits occurred at Weeks 4, 8, and 12, followed by quarterly visits thereafter.

Inclusion criteria

Subjects were 18 to 80 years-old and had an established diagnosis of PAH that was either idiopathic or familial, collagen vascular disease-associated, associated with human immunodeficiency virus (HIV) infection, induced by anorexigens/toxins; or associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥1 year). Previous right heart catherization with findings consistent with PAH (pulmonary artery pressure mean [PAPm] ≥25 mmHg (at rest), pulmonary capillary wedge pressure [PCWP] or left ventricular end diastolic pressure [LVEDP] ≤15 mmHg, and pulmonary vascular resistance [PVR] >3 WU) and an echocardiograph excluding left heart disease were also required. Pulmonary function test

results confirmed a total lung capacity (TLC) at least 60% of predicted value, and a forced expiratory volume at 1 second (FEV_1) at least 50% of predicted value.

At the screening, subjects were WHO FC III or IV, able to walk unassisted (oxygen use allowed), had a 6-Minute Walk Distance (6MWD) of ≥100 m, and had declining or unsatisfactory clinical response to their current PAH therapy. Subjects receiving non-prostanoid Food and Drug Administration (FDA)-approved PAH therapies were stable on their current dose for at least 30 days prior to the baseline visit. Women of child-bearing potential were practicing abstinence or using 2 highly effective methods of contraception.

Prior to the baseline visit, subjects had completed 90 days of inhaled treprostinil treatment with a stable dose for at least 30 days to be eligible for randomization. During the baseline visit, subjects were confirmed as WHO FC III or IV with a declining or unsatisfactory clinical response to inhaled treprostinil therapy.

Exclusion criteria

Subjects were excluded for previous experience with beraprost, BPS-314d, or use of any investigational drug, device, or therapy within 30 days of the baseline visit or during the study. Any musculoskeletal disease, active hemorrhagic condition, or a history of interstitial lung disease (some exceptions made for collagen vascular disease) were excluded. Women who were pregnant or lactating were also excluded from consideration.

Primary endpoint

The primary endpoint was a comparison of esuberaprost to placebo added to inhaled treprostinil, as measured by time to clinical worsening. Clinical worsening was defined as death, hospitalization due to worsening PAH, use of parenteral prostacyclin, disease progression, or

unsatisfactory long-term clinical response. Secondary endpoints were measured at each clinical visit and included change from baseline 6MWD, Borg dyspnea score, WHO FC, and N-terminal pro-brain natriuretic peptide.

Table S1. TRIUMPH cohort baseline characteristics

Baseline Characteristic	TRIUMPH Sub-group (N=148)	TRIUMPH Inhaled Treprostinil (N=69)	TRIUMPH Placebo (N=79)
Age, years (mean [range])	54 (18 to 75)	57 (20 to 75)	53 (18 to 75)
Males >60 years, n (%)	8 (5)	5 (7)	3 (4)
Females, %	83	80	86
Etiology, n (%)			
Idiopathic or familial PAH	78 (53)	37 (54)	41 (52)
Collagen vascular disease	51 (35)	23 (33)	28 (35)
Other	19 (13)	9 (13)	10 (13)
Background PAH Therapy, %			
ERA	68	64	72
PDE5-I	32	36	28
REVEAL 2.0			
RRS, Mean ± SD	7.36 ± 2.2	7.38 ± 2.2	7.34 ± 2.1
Risk stratum, % (low/intermediate/high)	35/31/35	35/28/38	34/34/32
French Noninvasive Number of low risk criteria, % (0/1/2)	66/32/2	64/35/1	67/30/3
6MWD (m), median (IQR)	352 (298, 404)	347 (295, 395)	356 (300, 410)
≥440, n (%)	10 (7)	2 (3)	8 (10)
320 to <440, n (%)	91 (62)	45 (65)	46 (58)
165 to <320, n (%)	47 (32)	22 (32)	25 (32)
NT-proBNP (pg/mL), median (IQR)	636 (215, 1483)	611 (218, 1393)	650 (214, 1515)
<300, n (%)	48 (32)	25 (36)	23 (29)
300 to <1100, n (%)	54 (37)	22 (32)	32 (41)
≥1100, n (%)	46 (31)	22 (32)	24 (30)
NYHA/WHO FC			
Class III, n (%)	144 (97)	67 (97)	77 (98)
Class IV, n (%)	4 (3)	2 (3)	2 (3)
Heart Rate, bpm			
>96, n (%)	15 (10)	8 (12)	7 (9)
≤96, n (%)	133 (90)	61 (88)	72 (91)
Systolic Blood Pressure, mmHg			
<110, n (%)	58 (39)	26 (38)	32 (41)
≥110, n (%)	90 (61)	43 (62)	47 (60)
Renal Insufficiency[a], n (%)	24 (16)	12 (17)	12 (15)

6MWD, 6-Minute Walk Distance; bpm, beats per minute; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; IQR, interquartile range; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PDE5-I, phosphodiesterase type 5 inhibitor; RRS, REVEAL 2.0 risk score; SD, standard deviation; sGC, soluble guanylate cyclase; WHO FC, World Health Organization Functional Class

a Renal insufficiency was defined as an eGFR <60 mL/min/1.73m^2.

Table S2. Change from baseline to Week 12 in REVEAL Lite 2.0 risk score[a] in TRIUMPH cohort

Study Group	Baseline	Week 12	
	Mean (SD)	Mean (SD) Change from Baseline	Mean Difference (SE) p-value
Inhaled Treprostinil (n=69)	5.90 (2.15)	-0.81 (1.87)	-0.90 (0.26) p=0.0008
Placebo (n=79)	5.91 (1.96)	0.09 (1.31)	

6MWD, 6-Minute Walk Distance; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; SE, standard error; WHO, World Health Organization

a REVEAL Lite 2.0 risk score was calculated with the following: demographics, comorbidities (eGFR), WHO Functional Class, vital signs, 6MWD, and NT-proBNP. Higher values indicate greater risk for clinical worsening or mortality.

Note: No data were imputed. P-values were obtained from 2-sample t-test.

Table S3. Baseline characteristics by change in REVEAL risk category at Week 12/16 in the combined group

Baseline Characteristic	Improved to REVEAL Low Risk Category (N=30)	Maintained REVEAL Intermediate/High Risk or Worsened REVEAL Category (N=103)	P-Value
Age (years), mean (range)	54 (25 to 75)	58 (18 to 78)	p=0.166
Males >60 years, n (%)	3 (10)	13 (13)	p=1.0
Females, n (%)	23 (77)	81 (79)	p=0.818
Etiology, n (%)			
Idiopathic or familial PAH	18 (60)	52 (51)	p=0.564
Collagen vascular disease	9 (30)	42 (41)	
Other	3 (10)	9 (9)	
Background PAH Therapy, n (%)			
None	2 (7)	7 (7)	p=0.826
ERA	16 (53)	49 (48)	
PDE5-I	7 (23)	33 (32)	
ERA + PDE5-I	5 (17)	14 (14)	
6MWD (m), median (IQR)	331 (293, 415)	324 (259, 371)	p=0.083
6MWD Category			
≥440, n (%)	3 (10)	3 (3)	p=0.279
320 to <440, n (%)	14 (47)	54 (52)	
165 to <320, n (%)	13 (43)	41 (40)	
<165, n (%)	-	5 (5)	
NT-proBNP (pg/mL), median (IQR)	457 (349, 1096)	1010 (593, 2505)	p<0.001
NT-proBNP (pg/mL) Category			
<300, n (%)	5 (17)	11 (11)	p=0.06
300 to <1100, n (%)	18 (60)	43 (42)	
≥1100, n (%)	7 (23)	49 (48)	
NYHA/WHO FC			
Class III, n (%)	29 (97)	99 (96)	p=1.0
Class IV, n (%)	1 (3)	4 (4)	
Heart Rate (bpm), median (IQR)	78 (72, 92)	81 (74, 88)	p=0.579
Heart Rate (bpm) Category			
>96, n (%)	7 (23)	6 (6)	p=0.01
≤96, n (%)	23 (77)	97 (94)	
SBP (mmHg), median (IQR)	111 (100, 131)	116 (105, 130)	p=0.332
SBP (mmHg) Category			
<110, n (%)	13 (43)	35 (34)	p=0.348
≥110, n (%)	17 (57)	68 (66)	

6MWD, 6-Minute Walk Distance; bpm, beats per minute; ERA, endothelin receptor antagonist; IQR, interquartile range; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PDE5-I, phosphodiesterase type 5 inhibitor; SBP, systolic blood pressure; WHO FC, World Health Organization Functional Class

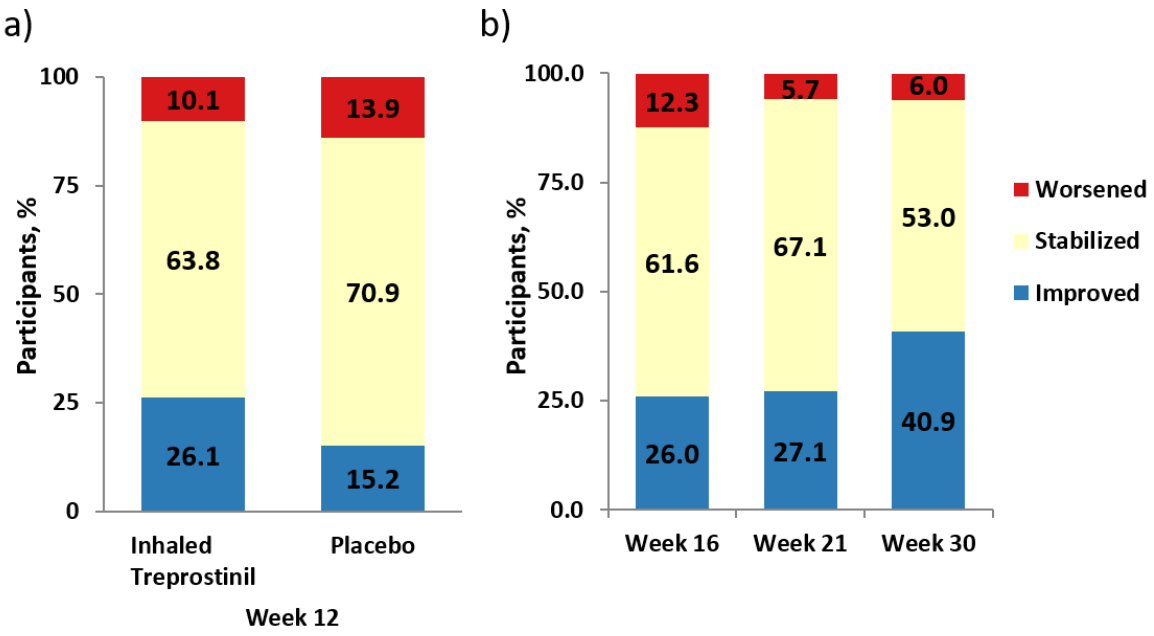

Figure S1. Change in REVEAL 2.0 risk stratum sensitivity analysis coding all patients with idiopathic/familial as "familial," rather than the primary analysis in the current study coding as "idiopathic." a) TRIUMPH inhaled treprostinil and placebo Week 12 and b) BEAT iTNP cohort Weeks 16, 21, and 30. "Improved" indicates a shift from a higher to lower risk stratum, "Stabilized" indicates the same stratum, and "Worsened" indicates a shift from a lower to higher risk stratum. REVEAL 2.0 analysis assuming familial PAH added 2 points to the risk score for subjects classified as idiopathic/familial PAH, the current analysis omitted this generalized category. Assuming familial PAH, the baseline REVEAL 2.0 categories for the BEAT iTNP cohort were 17.8% low, 34.2% intermediate, and 47.9% high risk. For TRIUMPH, the baseline REVEAL 2.0 categories using this method were 26.1% low, 27.5% intermediate, and 46.4% high risk; the placebo cohort was 19.0% low, 34.2% intermediate, and 46.8% high risk at baseline.

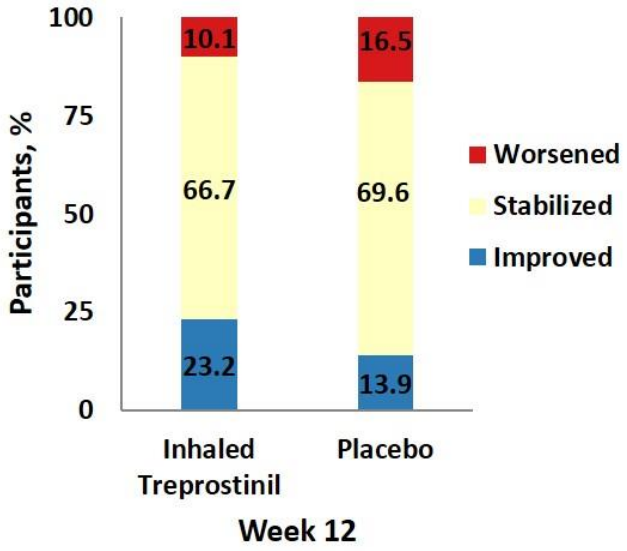

Figure S2. Change in REVEAL Lite 2.0 risk stratum from baseline to TRIUMPH Week 12. "Improved" indicates a shift from a higher to lower risk stratum, "Stabilized" indicates the same stratum, and "Worsened" indicates a shift from a lower to higher risk stratum.

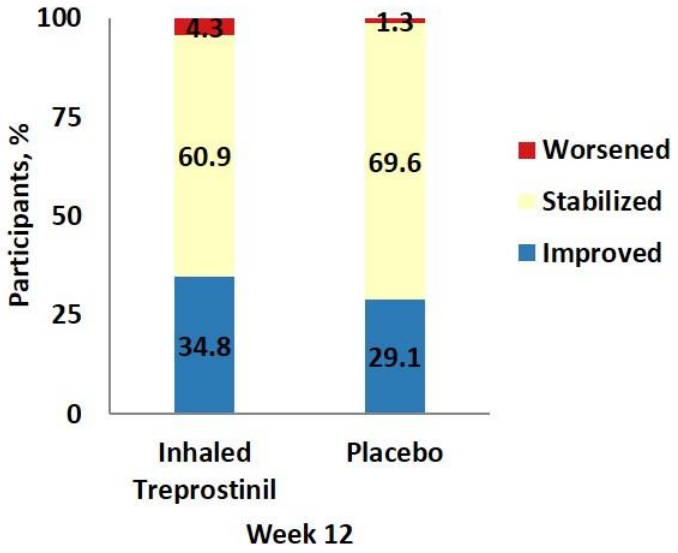

Figure S3. Change in number of low-risk criteria from baseline to TRIUMPH Week 12. "Improved" indicates any increase in the number of low risk criteria, "Stabilized" indicates the same number of risk criteria, and "Worsened" indicates any decrease in the number of low risk criteria.

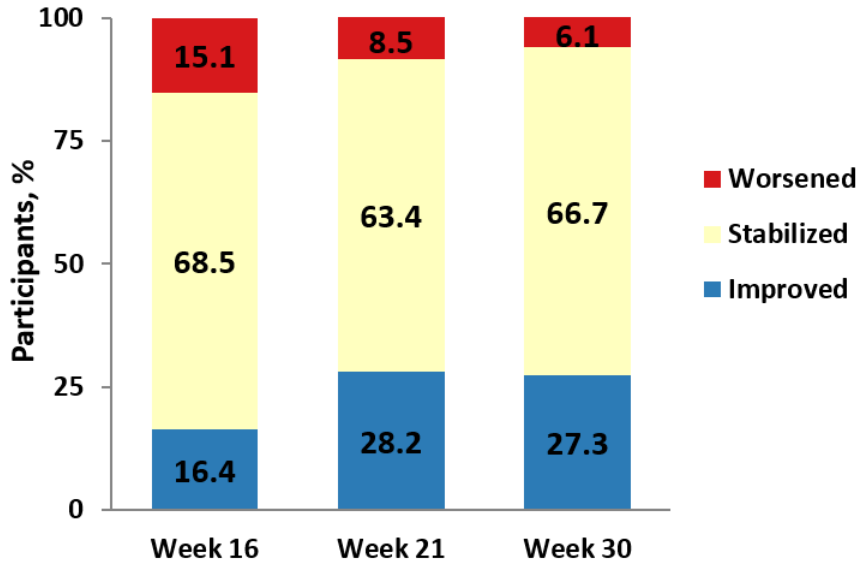

Figure S4. Change in REVEAL Lite 2.0 risk stratum from baseline to BEAT iTNP Week 16, Week 21, and Week 30. "Improved" indicates a shift from a higher to lower risk stratum, "Stabilized" indicates the same stratum, and "Worsened" indicates a shift from a lower to higher risk stratum.

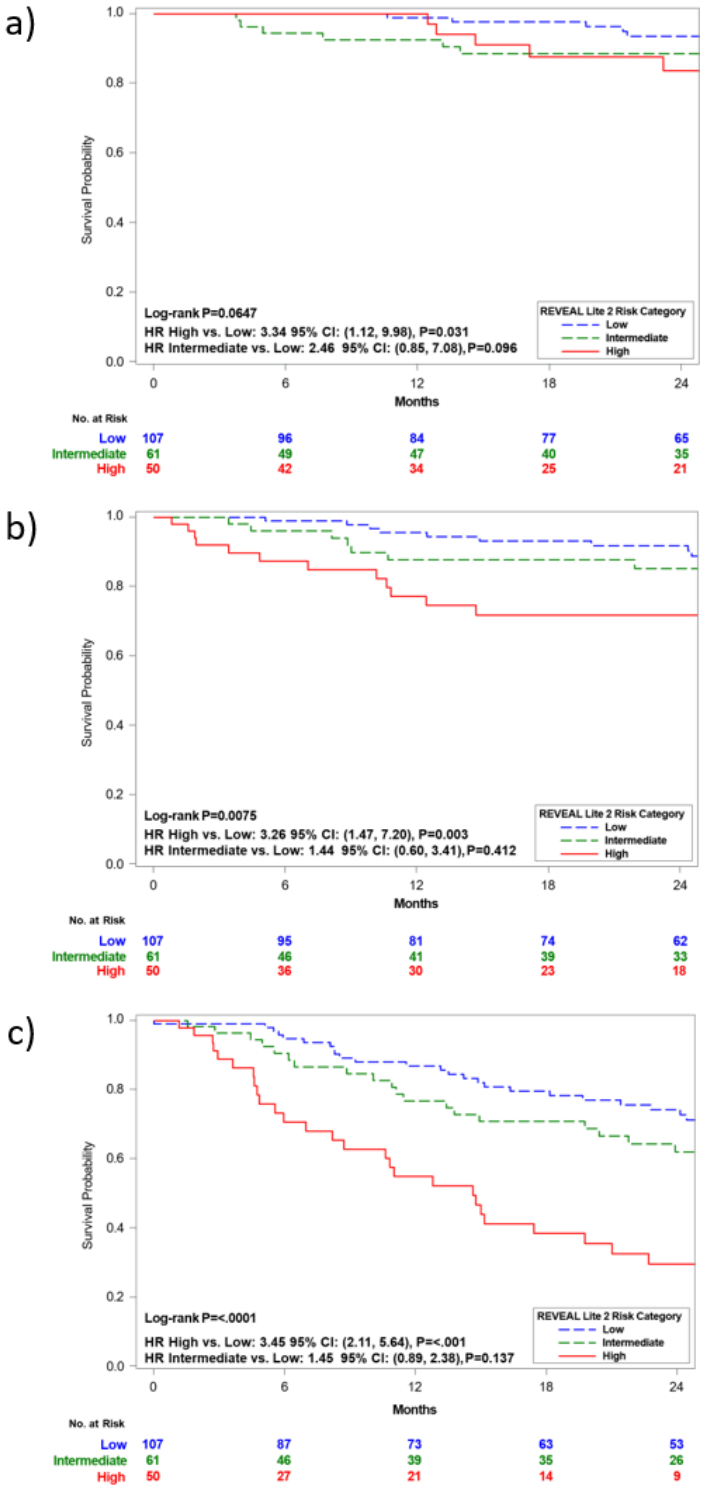

Figure S5. Kaplan-Meier estimate for a) overall survival b) PAH-related hospitalization-free survival and c) clinical worsening-free survival by REVEAL Lite 2.0 risk stratum at Week 12/16 for the pooled TRIUMPH and BEAT iTNP cohorts. A score from ≤5 was considered "Low" risk, 6 to 7 was considered "Intermediate" risk, and a score of 8 or higher was considered "High" risk.

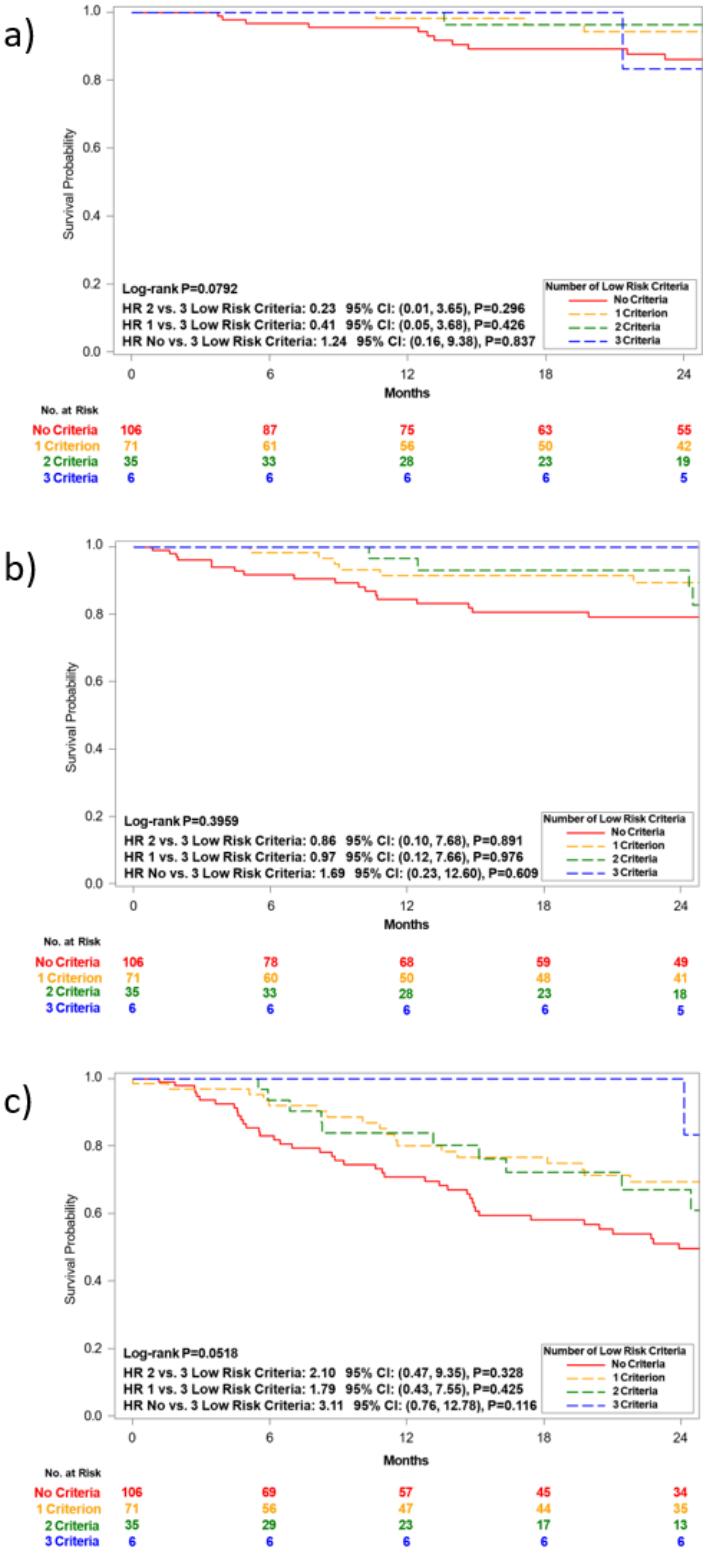

Figure S6. Kaplan-Meier estimate for a) overall survival b) PAH-related hospitalization-free survival and c) clinical worsening-free survival by number of low risk criteria at Week 12/16 for the pooled TRIUMPH and BEAT iTNP cohorts.