Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44. DOI: 10.1056/NEJMoa1413687

SUPPLEMENTARY APPENDIX

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Supplementary Statistical Methods

Primary End Point

Statistical significance of the primary efficacy end point was tested using the stratified log-rank test. A Cox proportional-hazards regression model was used to calculate the hazard ratio and 95% confidence interval. Kaplan Meier curves were used to illustrate treatment differences over time in the primary efficacy end point. Supportive end points, such as the primary efficacy end point excluding the unsatisfactory clinical response component and the individual components of the primary efficacy end point, were analyzed in the same manner as the primary efficacy end point. For the time-to-event analyses, participants who withdrew from the study were censored at their last known date in the study; however, if an event of hospitalization or death was reported after withdrawal, it was included in the analyses.

Primary end point events reported after the final assessment visit were not included in the primary analysis, but were included in a sensitivity analysis. The study design took into account that following each participant's final assessment visit, investigators would need to make decisions regarding future treatment, and future treatment decisions would be informed by knowing what treatment participants had been randomized to. Therefore, investigators would need to be unblinded at a participant's end-of-study visit so they could provide appropriate treatment for each participant upon study completion. To accommodate this, we included 2 database freezes. The first database freeze was planned after the last randomized participant had received ≥24 weeks of therapy and the 105th adjudicated first clinical failure event was projected to have occurred in the primary analysis set. At that time, all participants were notified to return

for a final assessment visit or their Week 24 visit, whichever was later. The database was frozen for each participant's visit-based data through the final assessment visit. The primary analysis was performed on these data. Participants then returned to the clinic for their end-of-study visit, the investigator was unblinded and participants were treated per investigator discretion. Following the last participant's end-of-study visit, the database was frozen a second time, and locked. A sensitivity analysis was performed on these data also including events that occurred between the final assessment visit and the end-of-study visit.

Secondary End Points

If the comparison of the primary end point was statistically significant, the secondary end points were to be analyzed in an alpha-controlled sequential step-down manner. Secondary efficacy end points were measured at week 24 and were tested in the following order: change from baseline in N-terminal pro-brain natriuretic peptide levels; percentage of participants with a satisfactory clinical response; change from baseline in 6-minute walk distance; change from baseline in WHO functional class; and change from baseline in Borg dyspnea index.

N-terminal pro-brain natriuretic peptide levels were presented as the geometric mean and geometric mean ratio and analyzed using an analysis of covariance model and mixed models repeated measures with terms for treatment, etiology, WHO functional class, and baseline measurement. Change from baseline in WHO functional class (categorized as improved, no change, and deteriorated) was analyzed using the Cochran-Mantel-Haenszel test. The percentage of participants with a satisfactory clinical response

was analyzed as a binary end point using logistic regression with treatment, etiology and WHO functional class as covariates. Change in 6-minute walk distance and Borg dyspnea index were analyzed using the Wilcoxon rank-sum test stratified by etiology and WHO functional class.

Missing week 24 values for 6-minute walk distance and WHO functional class were assigned worst-rank scores if they were preceded by an adjudicated clinical failure event of death or hospitalization; otherwise they were imputed using a last observation carried forward (LOCF) approach. Sensitivity analyses using a model-based approach were also performed.

Post-hoc Analyses

Separate Analysis of Variance (ANOVA) models to test the existence of any evidence of a treatment difference for days on randomized medication, days on study or time to first hospitalization (all cause) were run. The ANOVA models included a term for treatment with adjustments for baseline etiology and WHO functional class.

The number (%) of participants with a hospitalization due to worsening pulmonary arterial hypertension or serious adverse event of hospitalization (all cause) were analyzed by the Chi-Square method.

Table S1. List of All Initial Trial Inclusion and Exclusion Criteria.

Inclusion Criteria	
1	Between 18 and 75 years of age, inclusive, at the Screening Visit.
2	Weigh ≥40 kg at the Screening Visit.
3	Have a diagnosis of PAH due to the following: a. idiopathic or heritable PAH b. PAH associated with: i. connective tissue disease (e.g., limited scleroderma, diffuse scleroderma, mixed CTD, systemic lupus erythematosus, or overlap syndrome) ii. drugs or toxins iii. HIV infection iv. congenital heart defects repaired greater than 1 year prior to screening (i.e., atrial septal defects, ventricular septal defects, and patent ductus arteriosus) NB: those with portopulmonary hypertension and PVOD are <u>NOT</u> eligible for the study.
4	Have a current diagnosis of being in WHO Functional Class II or III.
5	Participant with a diagnosis of HIV must have stable disease status. For this study, stable HIV status is defined as: v. No addition of medications for treatment of HIV for at least 8 weeks prior to screening vi. No active opportunistic infection during the Screening Period vii. No hospitalizations due to HIV for at least 4 weeks prior to screening.
6	Meet all of the following hemodynamic criteria by means of a RHC prior to screening: i. mPAP of ≥25 mmHg ii. PVR ≥240 dyne·sec/cm5 iii. PCWP or LVEDP of ≤15 mmHg.
7	Meet all of the following pulmonary function tests completed no more than 24 weeks before the Screening Visit: i. Total lung capacity (TLC) ≥60% of predicted normal and ii. Forced expiratory volume in one second (FEV1) ≥55% of predicted normal.

8	Walk a distance of ≥125m and ≤500m at the Screening Visit.
9	Participant, with or without supplemental oxygen, must have a resting arterial oxygen saturation (SaO2) ≥88% as measured by pulse oximetry at the Screening Visit.
10	Participant has not enrolled in an exercise training program for pulmonary rehabilitation within 12 weeks prior to the Screening Visit and must agree not to enroll in an exercise training program for pulmonary rehabilitation during the Screening Period and the first 24 weeks of the study. Participants enrolled in an exercise program for pulmonary rehabilitation 12 weeks prior to screening may enter the study if they agree to maintain their current level of rehabilitation for the first 24 weeks of the study.
11	Females of childbearing potential must agree to use 2 reliable methods of contraception from the Screening Visit until study completion and for at least 30 days following the last dose of investigational product.
12	Agree not to participate in a clinical study involving another investigational drug or device throughout this study.
13	Competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved ICF and must sign the form prior to the initiation of any study procedures.
Exclusion Criteria	
1	Received previous PAH therapy (PDE5i, ERA, chronic prostanoid*) within 4 weeks prior to the Screening Visit. *Chronic prostanoid use is considered >7 days of treatment
2	Received ERA treatment (e.g., bosentan or sitaxentan) or PDE5i treatment (e.g. Sildenafil) at any time AND discontinued due to tolerance issues <u>other than</u> those associated with liver function abnormalities.
3	Previously discontinued ambrisentan or tadalafil in either another clinical study or commercial product (Volibris/Letairis or Adcirca) for safety or tolerability reasons.
4	Known hypersensitivity to the Investigational Products, the metabolites, or formulation excipients.
5	Receiving intravenous inotropes within 2 weeks prior to the Screening Visit (e.g. dopamine, dobutamine).
6	Receiving treatment with a potent inhibitor of CYP3A4 (e.g. protease inhibitors, systemic ketoconazole, or systemic itraconazole).
7	Receiving treatment with a potent inducer of CYP3A4 (e.g. rifampicin).
8	Receiving calcium channel blockers or HMG-CoA reductase inhibitors (i.e., statins) on an unstable dose 4 weeks prior to the Screening Visit (to be eligible participants must not have changed their dose <4 weeks prior to the Screening

	Visit).
9	History of angina pectoris or other condition that was treated with long or short-acting nitrates <12 weeks of screening.
10	Serum ALT or AST lab value that is > 2xULN at the Screening Visit.
11	Serum bilirubin lab value that is >1.5xULN at the Screening Visit.
12	Severe renal impairment (creatinine clearance <30 mL/min) at the Screening Visit.
13	Severe hepatic impairment (Child-Pugh class C with or without cirrhosis) at the Screening Visit.
14	Clinically significant anemia in the opinion of the investigator.
15	Bleeding disorders or significant active peptic ulceration in the opinion of the investigator.
16	Uncontrolled hypertension (≥180/110 mmHg) at screening.
17	Severe hypotension (<90/50 mmHg) at screening.
18	Acute myocardial infarction within the last 90 days prior to screening.
19	Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or congestive cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; left ventricular outflow obstruction; symptomatic coronary artery disease; autonomic hypotension; or fluid depletion in the opinion of the investigator.
20	Past medical history of NAION.
21	Hereditary degenerative retinal disorder (e.g. retinitis pigmentosa).
22	Clinically significant fluid retention in the opinion of the investigator.
23	Cardiovascular, liver, renal, hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the investigator, may adversely affect the safety of the participant and/or efficacy of the investigational product or severely limit the lifespan of the participant other than the condition being studied.
24	Participant has a history of malignancies within the past 5 years, except for localized, non-metastatic basal cell carcinoma of the skin, in situ carcinoma of the cervix, or prostate cancer who is not currently or expected, during the study, to undergo radiation therapy, chemotherapy, and/or surgical intervention, or to initiate hormonal treatment.
25	Females who are pregnant or breastfeeding.
26	Demonstrated noncompliance with previous medical regimens.
27	Recent (within 1 year) history of abusing alcohol or illicit drugs.
28	Participated in a clinical study involving another investigational drug or device

	within 4 weeks before the Screening Visit.

Table S2. Inclusion and Exclusion Criteria As Per Initial Protocol and Revised Criteria As Per Subsequent Amendment.

Initial Protocol	**Revised Criteria**
Inclusion criteria: Confirmed diagnosis of PAH with:* - mPAP ≥25 mm Hg - PVR ≥240 dyne·sec/cm^5 - PCWP or LVEDP ≤15 mm Hg *Exclusion criteria:* No exclusions with regard to cardiovascular risk factors	*Inclusion criteria:* Confirmed diagnosis of PAH with:* - mPAP ≥25 mm Hg - PVR ≥300 dyne·sec/cm^5 - PCWP or LVEDP ≤12 mm Hg if PVR ≥300 to <500 dyne·sec/cm^5 - or PCWP or LVEDP ≤15 mm Hg if PVR ≥500 dyne·sec/cm^5 *Exclusion criteria:* Participants must not have ≥3 of the following HFpEF risk factors: - BMI ≥30 kg/m^2 - History of essential hypertension - Diabetes mellitus (any type) - Historical evidence of significant CAD established by any of the following: History of MI History of PCI

	Angiographic evidence of CAD (>50% stenosis in ≥1 vessel) Positive ST Previous CABG Stable angina

*Based on right heart catheterization before screening.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; LVEDP = left ventricle end diastolic pressure; MI = myocardial infarction; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCI = percutaneous coronary intervention; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; ST = stress test.

Table S3. Summary of Time to First All-Cause Hospitalization in the Primary Analysis Set (Baseline to Final Assessment Visit).

	Combination Therapy (n=253)	**Pooled Monotherapy (n=247)**	**Ambrisentan Monotherapy (n=126)**	**Tadalafil Monotherapy (n=121)**	**Total (N=500)**
Number (%) of participants with a hospitalization due to worsening PAH or SAE hospitalization (all cause)	94 (37%)	107 (43%)	56 (44%)	51 (42%)	201 (40%)
P-value*	–	0.16	0.17	0.35	
Time to first such hospitalization, days					
n	94	107	56	51	201
Mean	271	284	328	235	278
SD	267	238	268	192	252
P-value	–	0.75	0.15	0.38	
Number of such hospitalizations per participant year of exposure	0.30	0.37	0.36	0.38	0.33

*Chi-Square method vs combination therapy group.

Post-hoc analyses.

PAH = pulmonary arterial hypertension; SAE = serious adverse event.

Table S4. Sensitivity Analysis of Primary End Point at End of Study Visit (Primary Analysis Set).

Event	Combination Therapy (n=253)	Pooled Monotherapy (n=247)	Ambrisentan Monotherapy (n=126)	Tadalafil Monotherapy (n=121)
Participants with first event, n (%)	52 (21)	84 (34)	47 (37)	37 (31)
Death	13	11	3	8
Hospitalization for worsening PAH	10	32	19	13
Disease progression	12	16	12	4
Unsatisfactory long-term clinical response	17	25	13	12
Hazard ratio (combination vs each monotherapy group)	–	0.52	0.48	0.56
95% CI	–	0.37, 0.73	0.32, 0.71	0.37, 0.86
P-value	–	<0.001	<0.001	0.01

CI = confidence interval; PAH = pulmonary arterial hypertension.

This sensitivity analysis includes the primary end point events (to FAV) plus events that occurred between the final assessment visit and the end-of-study visit, reported after the first database freeze, when a number of investigators were unblinded to treatment assignment. See the explanation above.

Table S5. Summary of First Adjudicated Clinical Failure Event (Excluded from Primary Analysis Set).

Event	Combination Therapy (n=49)	Pooled Monotherapy (n=56)	Ambrisentan Monotherapy (n=26)	Tadalafil Monotherapy (n=30)
Participants with first event, n (%)	14 (29)	21 (38)	10 (38)	11 (37)
Death	4	4	3	1
Hospitalization for worsening PAH	1	6	3	3
Disease progression	5	5	1	4
Unsatisfactory long-term clinical response	4	6	3	3

PAH = pulmonary arterial hypertension.

Inferential analyses were not performed for the ex-primary analysis set due to the small size of this population.

Table S6. Analysis of the Primary End Point Excluding the Unsatisfactory Clinical Response Component (Primary Analysis Set).

Event	Combination Therapy (n=253)	Pooled Monotherapy (n=247)	Ambrisentan Monotherapy (n=126)	Tadalafil Monotherapy (n=121)
Participants with first event, n (%)	36 (14)	60 (24)	36 (29)	24 (20)
Hazard ratio (combination vs each monotherapy group)	–	0.51	0.44	0.61
95% CI	–	0.34, 0.78	0.28, 0.70	0.36, 1.03
P-value	–	0.001	<0.001	0.06

CI = confidence interval.

Table S7. Analysis of Time to First Adjudicated Primary End Point Event and Study Discontinuation (Primary Analysis Set).

Event	Combination Therapy (n=253)	Pooled Monotherapy (n=247)	Ambrisentan Monotherapy (n=126)	Tadalafil Monotherapy (n=121)
Participants with first event, n (%)	70 (28)	111 (45)	61 (48)	50 (41)
Hazard ratio (combination vs each monotherapy group)	–	0.54	0.51	0.57
95% CI	–	0.40, 0.73	0.36, 0.73	0.40, 0.82
P-value	–	<0.001	<0.001	0.002

CI = confidence interval.

This post-hoc sensitivity analysis adds study discontinuation as a 5th component to the primary end point, as time to first event analysis (primary end point components or discontinuation), and therefore assesses the impact of study discontinuation on the primary end point analysis. This table includes events occurring prior to the final assessment but reported after the first database freeze.

Table S8. Change From Baseline to Week 24 for 6MWD and WHO Functional Class (Primary Analysis Set).

End Point	Combination Therapy (n=253)	Pooled Monotherapy (n=247)	Ambrisentan Monotherapy (n=126)	Tadalafil Monotherapy (n=121)
6MWD change from baseline, m, median (Q1, Q3)*				
Week 24	n=229 52.50 (14.95, 90.00)	n=216 31.55 (-5.00, 67.50)	n=108 34.00 (-5.50, 66.45)	n=108 30.25 (-3.00, 67.50)
6MWD change from baseline (MMRM), m, mean*				
Week 24	n=229 51.74	n=216 27.26	n=108 21.21	n=108 33.30
P-value	–	<0.001	<0.001	0.01
WHO FC, n (%)*				
Week 24	n=233	n=220	n=109	n=111
Improved	89 (38)	80 (36)	41 (38)	39 (35)
No change	138 (59)	133 (60)	63 (58)	70 (63)
Deteriorated	6 (3)	7 (3)	5 (5)	2 (2)
P-value	–	0.66	0.63	0.82
WHO FC (MMRM)				
Week 24	n=233	n=220	n=109	n=111
Least-squares mean change from baseline	-0.4	-0.3	-0.4	-0.3

Mean difference (95% CI)		-0.0 (-0.1, 0.1)	-0.0 (-0.2, 0.1)	-0.0 (-0.2, 0.1)
P-value	–	0.46	0.62	0.48

*Data based on observed cases, no imputation.

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; MMRM = mixed models repeated measures; Q = quartile; WHO = World Health Organization.

Table S9. Summary of Safety Findings (Primary Analysis Set, on Randomized Treatment).

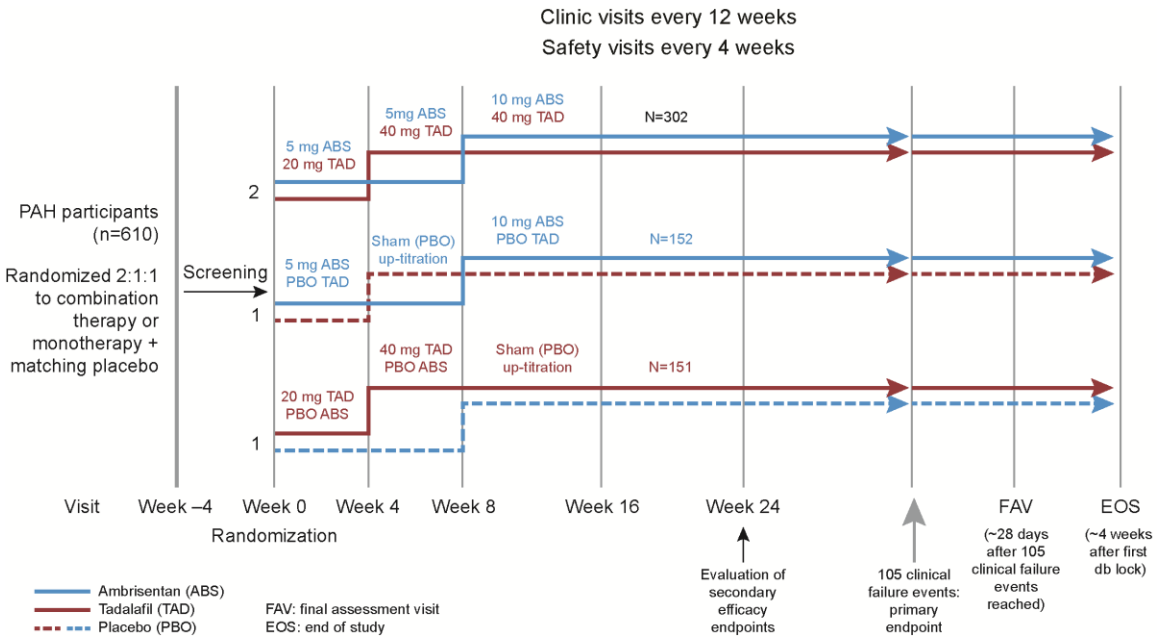
	Combination Therapy (n=253)	**Ambrisentan Monotherapy (n=126)**	**Tadalafil Monotherapy (n=121)**
Most common AE (≥10% in any group), n (%)			
Peripheral edema	115 (45)	41 (33)	34 (28)
Headache	107 (42)	41 (33)	42 (35)
Nasal congestion	54 (21)	19 (15)	15 (12)
Diarrhea	50 (20)	29 (23)	23 (19)
Dizziness	50 (20)	24 (19)	14 (12)
Dyspnea	44 (17)	22 (17)	20 (17)
Nausea	43 (17)	18 (14)	20 (17)
Cough	40 (16)	14 (11)	21 (17)
Flushing	38 (15)	18 (14)	11 (9)
Anemia	37 (15)	8 (6)	14 (12)
Nasopharyngitis	37 (15)	26 (21)	18 (15)
Pain in extremity	37 (15)	14 (11)	18 (15)
URTI	34 (13)	20 (16)	20 (17)
Arthralgia	32 (13)	17 (13)	19 (16)
Back pain	31 (12)	13 (10)	18 (15)
Fatigue	30 (12)	17 (13)	15 (12)
Dyspepsia	29 (11)	5 (4)	14 (12)

Palpitations	28 (11)	20 (16)	17 (14)
Vomiting	28 (11)	11 (9)	12 (10)
Bronchitis	27 (11)	5 (4)	10 (8)
Non-cardiac chest pain	27 (11)	10 (8)	8 (7)
Myalgia	23 (9)	12 (10)	15 (12)
UTI	18 (7)	9 (7)	15 (12)
Pulmonary hypertension*	12 (5)	13 (10)	9 (7)
Other AEs of clinical interest			
Hypotension	20 (8)	9 (7)	9 (7)
Syncope	13 (5)	7 (6)	10 (8)
AEs leading to treatment discontinuation			
Any	31 (12)	14 (11)	14 (12)
Most common			
Dyspnea	5 (2)	0	1 (<1)
Peripheral edema	4 (2)	3 (2)	1 (<1)
Serious AEs			
Any	92 (36)	45 (36)	50 (41)
Most common			
Pulmonary hypertension*	11 (4)	11 (9)	9 (7)
Pneumonia	11 (4)	7 (6)	4 (3)

*In each case, the investigator reported the events using additional text not captured in the preferred term, describing this as worsening of pulmonary hypertension. However, an AE report of worsening pulmonary hypertension does not necessarily become a primary end point event, which has specific criteria.

AE = adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

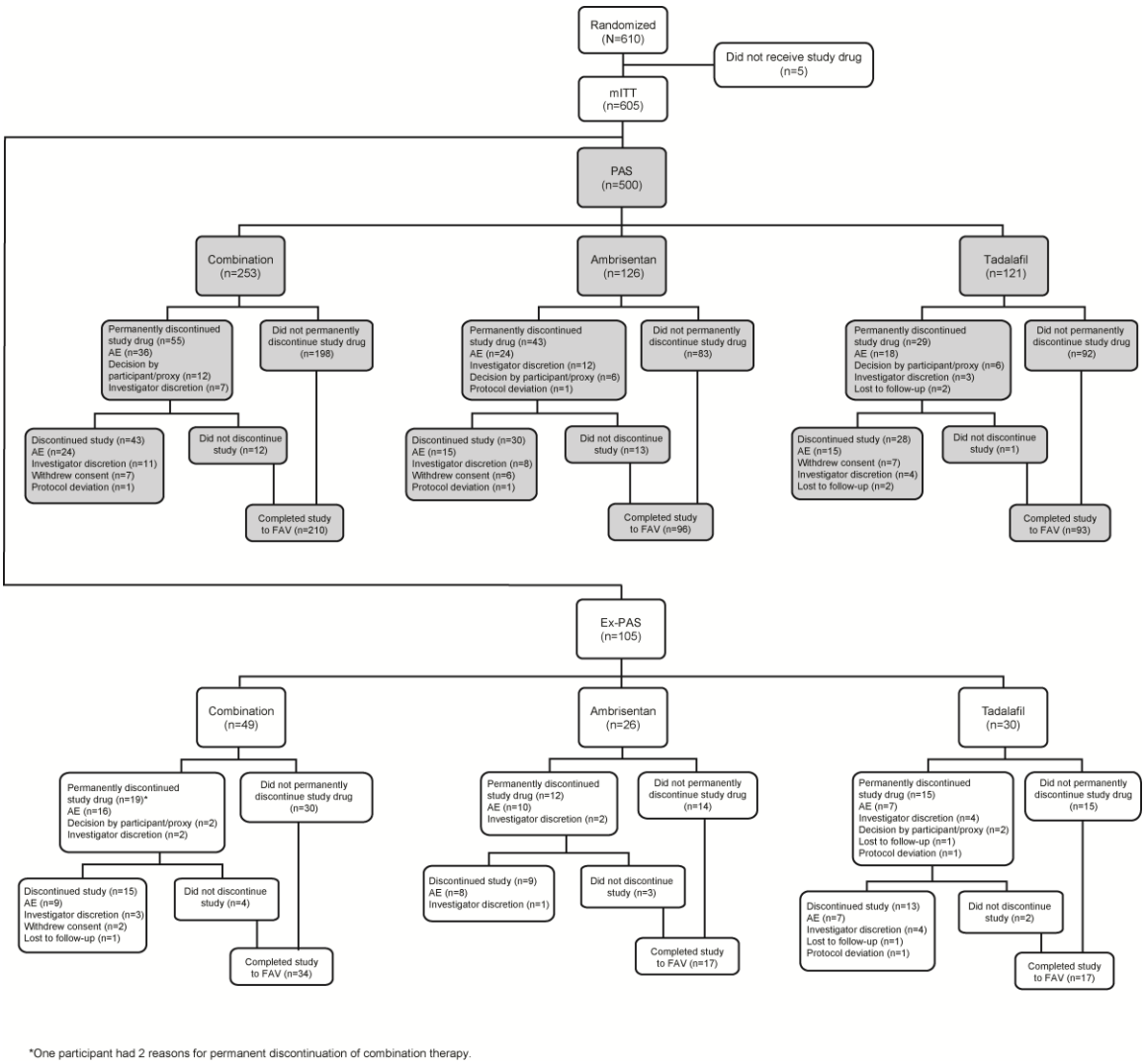
Figure S1. Study Design.



Legend: Participants received 5-mg ambrisentan tablets and 20-mg tadalafil tablets together or as monotherapy. Matching placebo tablets were administered to maintain blinding. Ambrisentan was given at a dose of 5 mg once daily for the first 8 weeks and 10 mg once daily thereafter; tadalafil was administered at a dose of 20 mg once daily for the first 4 weeks and 40 mg once daily thereafter. Participants received a minimum of 24 weeks of therapy. At the estimated time of the occurrence of the 105th event in the primary analysis set, all participants were notified to return for the final assessment visit (FAV) within 28 days or for their week 24 visit, whichever occurred later. The database was frozen for each participant's visit-based data through FAV. The primary analysis of the primary end point was performed on the events occurred up to the FAV. Blinded treatment was continued following the FAV, after which the participants returned within 4 weeks for the end-of-study (EoS) visit and were then unblinded. Also the events occurred between the FAV and the EoS visit were recorded and adjudicated. Following

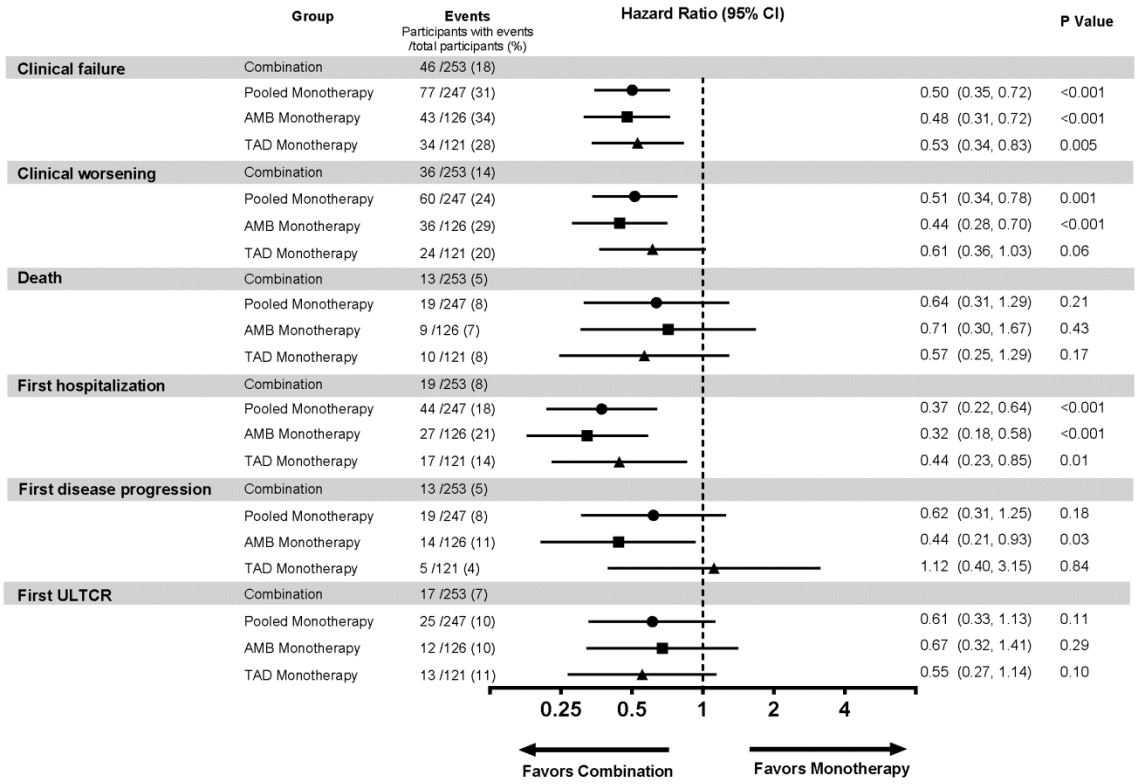
the last participant's EoS visit, the database was locked for all visits. A sensitivity analysis was performed on these data, also including events that occurred between the FAV and the EoS visit (Table S4). 6MWD = 6-minute walk distance; db = database; PAH = pulmonary arterial hypertension.

Figure S2. Participant Disposition.



AE = adverse event; FAV = final assessment visit; mITT = modified intention to treat; PAS = primary analysis set; Ex-PAS = excluded from the primary analysis set

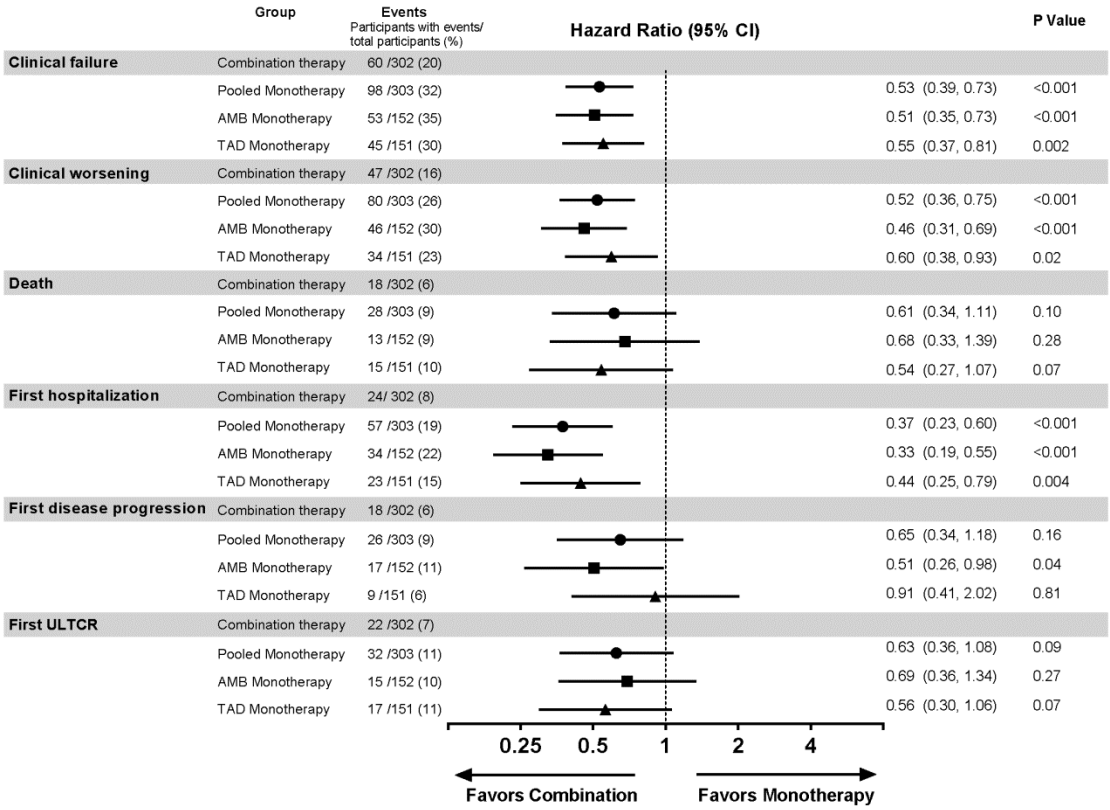
Figure S3. Forest Plot of Primary End Point (Clinical Failure) and Its Components in the Primary Analysis Set. Clinical Worsening Is Also Included.*



Hazard ratios = combination vs pooled monotherapy group and vs each monotherapy group. CI = confidence interval; ULTCR = unsatisfactory long-term clinical response.

***Clinical worsening is defined as the first occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, or disease progression.**

Figure S4. Forest Plot of Primary End Point (Clinical Failure) and Its Components in the Modified Intention-to-Treat Population. Clinical Worsening Is Also Included.*

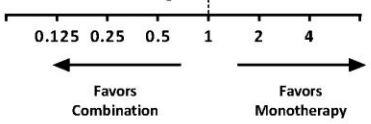


Hazard ratios = combination vs pooled monotherapy group and vs each monotherapy group. CI = confidence interval; ULTCR = unsatisfactory long-term clinical response.

*** Clinical worsening is defined as the first occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, or disease progression.**

Figure S5. Forest Plot of the First Adjudicated Primary End Point (Clinical Failure) Event by Etiology, Baseline World Health Organization Functional Class, Baseline Age, Baseline 6-Minute Walk Distance, Region, and Gender. Primary Analysis Set.

Subgroup	No. of Participants	Combination Therapy	Pooled Monotherapy	Hazard Ratio (95% CI)	P Value	P Value for Interaction
		Participants with events /total participants (%)				
Etiology						0.66
IPAH/HPAH	279	25 /134 (19)	46 /145 (32)	0.54 (0.33, 0.87)	0.01	
APAH	221	21 /119 (18)	31 /102 (30)	0.45 (0.26, 0.79)	0.005	
Baseline WHO FC						0.08
WHO FC II	155	4 /76 (5)	17 /79 (22)	0.21 (0.07, 0.63)	0.005	
WHO FC III	345	42 /177 (24)	60 /168 (36)	0.58 (0.39, 0.86)	0.006	
Age at Baseline						0.26
< 57 years	244	13 /124 (10)	31 /120 (26)	0.37 (0.19, 0.70)	0.002	
>= 57 years	256	33 /129 (26)	46 /127 (36)	0.58 (0.37, 0.91)	0.02	
Baseline 6MWD						0.41
< 363.7 m	250	35 /129 (27)	51 /121 (42)	0.54 (0.35, 0.83)	0.005	
>= 363.7 m	250	11 /124 (9)	26 /126 (21)	0.38 (0.19, 0.77)	0.007	
Region						0.92
North America	228	22 /116 (19)	34 /112 (30)	0.51 (0.30, 0.87)	0.01	
Rest of World	272	24 /137 (18)	43 /135 (32)	0.51 (0.31, 0.83)	0.008	
Gender						0.68
Female	388	32 /188 (17)	61 /200 (31)	0.47 (0.31, 0.73)	<0.001	
Male	112	14 /65 (22)	16 /47 (34)	0.58 (0.28, 1.19)	0.14	



Hazard ratios = instantaneous risk (independent of duration of treatment exposure) of a primary end point event when receiving combination vs pooled monotherapy. A test for interaction between subgroup and treatment was performed to enable detection of evidence of differential treatment benefit between subgroup levels. 6MWD = 6-minute walk distance; APAH = pulmonary arterial hypertension associated with a connective tissue disease, drugs or toxins, human immunodeficiency virus (stable disease status), or repaired congenital heart defects; BL = baseline; CI = confidence interval; HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; WHO FC = World Health Organization functional class.

List of Investigators

The AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertensION (AMBITION) study included the following principal investigators and study sites: *Australia* – Royal Prince Alfred Hospital, Camperdown, New South Wales: T. Corte, D. Celermajer, P.P. Youssef. St Vincents Hospital, Darlinghurst, New South Wales: A. Keogh. Prince Charles Hospital, Chermside, Queensland: F.D. Kermeen. Royal Hobart Hospital, Hobart, Tasmania: D. Kilpatrick*. Royal Perth Hospital, Perth, Western Australia: M.A. Lavender*. The Alfred Hospital, Melbourne, Victoria: T.J. Williams*. *Austria* – Medizinische Universität Innsbruck, Universitätsklinik für Innere Medizin VI, Innsbruck: C. Kaehler. Univ. Clinic for Internal Medicine II / Cardiology, Vienna: I.M. Lang. *Belgium* – Universitair Ziekenhuis Gasthuisberg, Leuven: M. Delcroix. Cliniques Universitaires de Bruxelles - Hôpital Erasme, Bruxelles: J.L. Vachiery. *Canada* – Health Sciences Centre, Respiratory Hospital, Winnipeg, Manitoba: Z. Bshouty. Toronto General Hospital, Toronto, Ontario: J. Granton. Peter Lougheed Center, Respiratory Research, Calgary, Alberta: N. Hirani. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, Québec: S. Provencher. Vancouver General Hospital, The Lung Centre, Vancouver, British Columbia: J.R. Swiston. *France* – CHRU de Montpellier - Hôpital Arnaud de Villeneuve, Montpellier: A. Bourdin. CHU de Nancy - Hôpital pour Adultes de Brabois Pneumologie, Vandoeuvre-les-Nancy: J.F. Chabot. Hôpital Louis Pradel, Lyon: V. Cottin. CHRU de Lille - Hôpital Cardiologique, Lille: P. De Groote. CHU de Bordeaux - Hôpital Haut-Lévêque, Pessac: C. Dromer. CHU de Brest - Hôpital de la Cavale Blanche, Brest: I. Frachon*. CHU la Réunion, Saint Pierre: F. Paganin. CHU de Grenoble - Hôpital Albert Michallon, La Tronche: C. Pison. CHU de Marseille - Hôpital Nord, Marseille: M. Reynaud-Gaubert. Hôpital Kremlin Bicêtre, Le Kremlin-Bicêtre: G. Simonneau. CHU de Toulouse - Hôpital Larrey, Toulouse: L. Tetu. *Germany* – Universitaetsklinikum Greifswald, Greifswald, Mecklenburg-Vorpommern: R. Ewert. Universitaetsklinikum Giessen, Giessen, Hessen: H.A. Ghofrani. Thoraxklinik Heidelberg gGmbH, Heidelberg, Baden-Wuerttemberg: E. Grünig. Missionsaerztliche Klinik Würzburg GmbH, Wuerzburg, Bayern: M. Held. Universitaetsklinikum Carl Gustav Carus Dresden, Dresden, Sachsen: G. Hoeffken. Medizinische Hochschule Hannover, Hannover, Niedersachsen: M.M. Hoeper. Universitaetsklinikum Eppendorf,

Hamburg, Hamburg: H.F.E. Klose. Universitaetsklinikum Regensburg, Regensburg, Bayern: T.J. Lange, M.W. Pfeifer. Klinikum Grosshadern, Muenchen, Bayern: C. Neurohr. DRK Kliniken Berlin Koepenick, Berlin, Berlin: C. Opitz. Klinikum der Universitaet Koeln, Koeln, Nordrhein-Westfalen: S. Rosenkranz. Universitaetsklinikum Bonn Medizinische Klinik II, Bonn, Nordrhein-Westfalen: D. Skowasch. Universitaetsklinikum Freiburg, Freiburg, Baden-Wuerttemberg: S. Sorichter. Klinikum Loewenstein GmbH, Loewenstein, Baden-Wuerttemberg: G. Staehler. Universitaetsklinikum des Saarlandes, Homburg, Saarland: H. Wilkens. Universitaetsklinikum Leipzig, Leipzig, Sachsen: H.R.W. Wirtz. *Greece* – University General Hospital "ATTIKON", Athens: A. Anthi. Onassis Cardiac Surgery Center, Athens: G. Athanasopoulos. Genaral Hospital of Kavala, Kavala: K. Blamis*. General University Hospital of Alexandroupolis, Alexandroupolis: D. Bouros*. University Hospital of Heraklion, Heraklion, Crete: D. Georgopoulos*. University General Hospital of Alexandroupolis, Alexandroupolis: S. Konstantinides*. G. Papanikolaou Hospital, Thessaloniki: I. Stanopoulos*. "Ahepa" University General Hospital of Thessaloniki, Thessaloniki: I. Styliadis. *Italy* – Azienda Ospedaliero-Universitaria Policlinico S. Orsola Malpighi, Bologna, Emilia-Romagna: N. Galiè. Fondazione Toscana "G. Monasterio" - CNR Regione Toscana, Pisa, Toscana: C. Marini. Azienda Ospedaliera Universitaria Vittorio Emanuele, Ferrarotto, Santo Bambino, U.O. di Cardiologia, Catania, Sicilia: M. Mulè, G.P. Ussia. Azienda Ospedaliera "G.Brotzu", Cagliari, Sardegna: M. Porcu. Policlinico Umberto I - Università La Sapienza, Roma, Lazio: C.D. Vizza. *Japan* – Kyushu University Hospital, Fukuoka: K. Abe, T. Kishi. The University of Tokyo Hospital, Tokyo: M. Hatano, A. Yao. Hokkaido University Hospital, Hokkaido: I. Tsujino*. Hamamatsu University School of Medicine, University Hospital, Shizuoka: H. Watanabe*. *Netherlands* – Academisch Ziekenhuis Maastricht, Maastricht: K.A. Boomars*. Erasmus MC, Rotterdam: L. Van Den Toorn. Vrije Universtiteit Medical Centre, Amsterdam: A. Vonk-Noordegraaf. *Spain* – Hospital Clinic i Provincial de Barcelona, Barcelona: J.A. Barberá. Hospital Universitario Son Espases, Palma de Mallorca: M. Carrera Lamarca*. Hospital Virgen del Rocío, Sevilla: M.J. Del Castillo Palma*. Hospital Doce de Octubre, Madrid: M.A. Gómez Sánchez. Hospital Virgen de la Salud, Toledo: M. Lázaro Salvador. Hospital La Fe, Valencia: R. López Reyes, D.

Nauffal Manzur. Hospital Carlos Haya, Málaga: J. Merino Verdugo. Complejo Hospital Clinico Universitario de Santiago de Compostela, A Coruna: P. Rigueiro Veloso*. Hospital Vall d'Hebrón, Barcelona: A. Román Broto. Hospital Reina Sofía, Córdoba: F. Santos Luna*. Hospital Puerta de Hierro, Madrid: J. Segovia Cubero. Hospital Ramón y Cajal, Madrid: A. Sueiro Bendito*. Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat: J. Valldeperas Combas. Hospital Marques de Valdecilla, Santander: F. Zurbano Goñi. *Sweden* – Universitetssjukhuset i Linköping, Linköping: L. Hubbert, K. Jansson. Skånes universitetssjukhus, Kliniken för hjärtsvikt och klaffsjukdom, Lund: G. Rådegran, B.L.V. Ekmehag. Sahlgrenska Universitetssjukhuset, Göteborg: B. Rundqvist, N. Selimovic. Umea University Hospital, Umeå: S. Söderberg. Akademiska Sjukhuset, Uppsala: G.G. Wikström. *United Kingdom* – Royal Free Hospital, London: J.G. Coghlan. Royal Hallamshire Hospital, Sheffield: D. Kiely. Golden Jubilee National Hospital, Clydebank: A.J. Peacock. Papworth Hospital, Cambridgeshire: J. Pepke-Zaba. Royal Brompton and Harefield NHS Foundation Trust, London: S.J. Wort*. *United States* – University of California Davis Medical Center, Sacramento, California: R. Allen. William Beaumont Hospital, Troy, Michigan: S.A. Allen. University of Colorado Cardiac and Vascular Center and University of Colorado Health Sciences Center, Aurora, Colorado: R.M. Aris. University of Colorado Health Sciences Center, Aurora, Colorado: D.B. Badesch. University of Florida Health Science Center, Jacksonville, Florida: A.A. Bajwa. Allegheny General Hospital, Pittsburgh, Pennsylvania: R.L. Benza. The Kirklin Clinic and Zeigler Research Building, Birmingham, Alabama: R.C. Bourge. Washington University School of Medicine, Saint Louis, Missouri: M.M. Chakinala. Midwest Heart Foundation, Oakbrook Terrace, Illinois: M.R. Costanzo. Temple Lung Center, Philadelphia, Pennsylvania: G.J. Criner*. The Oregon Clinic, Portland, Oregon: R.J. Cummings. Louisiana State University Health Sciences Center-New Orleans, New Orleans, Louisiana: B.P. DeBoisblanc. Sentara Cardiovascular Research Institute, Norfolk, Virginia: M.S. Eggert*. Intermountain Medical Center, Murray, Utah: C.G. Elliott. University Hospital and University of Cincinnati Physician Medical Arts Building, Cincinnati, Ohio: J.M. Elwing. The Carl and Edyth Lindner Center for Research and Education at the Christ Hospital, Cincinnati, Ohio: P.J. Engel. University of Southern Alabama Medical Centre, Mobile, Alabama: K.A. Fagan. Boston Medical

Center/Boston University School of Medicine Center Pulomonary, Boston, Massachusetts: H.W. Farber. Baystate Pulmonary & Critical Care Medicine, Springfield, Massachusetts: M.J.S. Farmer. Arizona Pulmonary Specialists, Limited, Phoenix, Arizona: J.P. Feldman. The Emory Clinic, Atlanta, Georgia: M.R. Fisher. University of Iowa Hospitals and Clinics, Iowa City, Iowa: A.K. Gerke, S. Hansdottir. Virginia Commonwealth University Medical Center, Richmond, Virginia: D.C. Grinnan. Clarian Health, Carmel, Indiana: W.L.F. Harvey. Shands at the University of Florida, Gainesville, Florida: A.M. Hassan. Tufts Medical Center, Boston, Massachusetts: N.S. Hill. Weill Cornell Medical Center, Perkin Center for Heart Failure, New York, New York: E.M. Horn. University of California, San Diego, La Jolla, California: H.S. Kim. Rhode Island Hospital, Providence, Rhode Island: J.R. Klinger. University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania: M.A. Mathier. Atlanta Institute for Medical Research, Inc., Decatur, Georgia: J.E. Michaelson*. Barnabas Health Newark Beth Israel Medical Center, Newark, New Jersey: C. Migliore, S.M. Studer. Saint Luke's - Roosevelt Hospital Center, New York, New York: R. Minkin. Central Florida Pulmonary Group P.A, Orlando, Florida: S.I. Mobin. Los Angeles Biomedical Research Institute at Harbor UCLA Medical Centre, Torrance, California: R.J. Oudiz. Cleveland Clinic Foundation, Cleveland, Ohio: J. Parambil, O.A. Minai. University of Maryland Medical Centre, Baltimore, Maryland: M.H. Park. Cleveland Clinic Florida - Weston, Weston, Florida: F.F. Rahaghi. University of Arizona Clinical and Translational Science (CATS) Research Center, Tucson, Arizona: F. Rischard. Vanderbilt University Medical Center, Nashville, Tennessee: I.M. Robbins. Atlanta Institute for Medical Research Inc., Decatur, Georgia: S.M. Rosenthal*. Columbia University Medical Center, New York, New York: E.B. Rosenzweig. University of Michigan Medical Center, Ann Arbor, Michigan: M. Rubenfire*. Baylor College of Medicine, Houston, Texas: Z. Safdar. University of Kansas Medical Center, Kansas City, Kansas: L.G. Satterwhite, T. Williamson. Wayne State University, Detroit Medical Centre, Detroit, Michigan: G. Saydain. West Los Angles VA Healthcare Center, Los Angeles, California: S. Shapiro. Morristown Memorial Hospital, Morristown, New Jersey: F.W. Smart*. Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania: K.A. Smith, P.R. Forfia. OSU Martha Morehouse Medical Plaza, Columbus, Ohio: N. Sood. Scott & White Memorial Hospital

and Clinic, Temple, Texas: C. Spradley. Beth Israel Medical Center, New York, New York: R. Sulica*. North Shore - LIJ Health System, New Hyde Park, New York: A. Talwar. University of Texas Southwestern Medical Center at Dallas, Dallas, Texas: F. Torres. Asheville Cardiology Associates, Asheville, North Carolina: B.H. Trichon. Pulmonary Disease Specialist Research, Kissimmee, Florida: J.A. Urdaneta-Jaimes. Brigham and Women's Hospital, Boston, Massachusetts: A.B. Waxman. University of Virginia Medical Center, Charlottesville, Virginia: M.M. Weder*. University of Rochester Medical Center, Rochester, New York: R.J. White. Creighton University Medical Centre, Omaha, Nebraska: T.O. Wichman, D. Schuller. Maine Medical Center, Portland, Maine: J.A. Wirth. St Luke's Medical Center, Milwaukee, Wisconsin: D.L. Zwicke.

*No participants randomized.

Independent Data Monitoring Committee Members

Maurice Beghetti, MD, Hopital Cantonal des Enfants, Geneva, Switzerland; Bruce Brundage, MD, 187 Madrid Ave., Palm Desert, California, United States (Nov-Apr) and 65740 Pronghorn Estates Dr., Bend, Oregon, United States (May-Oct); Sean Gaine, MD, Mater Hospital, Dublin, Ireland; Michael McGoon, MD, Mayo Clinic, Rochester, Minnesota, United States; Dr. Ian Ford, Robertson Centre for Biostatistics, Glasgow, Scotland.

Clinical End Point Adjudication Committee (CEAC) Members

CEAC chair: J. Simon Gibbs, MD, Hammersmith Hospital, National Pulmonary Hypertension Service,
Department of Cardiology, London, United Kingdom.

CEAC members: Teresa De Marco, MD, Director of Heart Transplantation, University of California, San Francisco, San Francisco, California, United States; Horst Olschewski, MD, PhD, Director, Division of Pulmonology, Department of Internal Medicine, Medical University of Graz, Graz, Austria.