Positive Predictors for Response to Ambrisentan Combination Therapy in Pulmonary Arterial Hypertension

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Summary
The AMBITION study (NCT01178073) provided the first long-term clinical evidence for initial combination therapy with ambrisentan and tadalafil in patients with pulmonary arterial hypertension (PAH). Nevertheless, predictors of treatment response were not assessed.

To identify predictors for response to initial combination therapy, we examined data from 302 patients with PAH (World Health Organization Functional Class II or III) who received initial combination therapy from the modified intention-to-treat population of the AMBITION study (n = 605). A responder was defined as not having undergone a clinical failure event. Univariate and multivariate analyses were performed. Multivariate logistic regression with interactive backward selection was used to assess the independent association of potential predictors with response.

Treatment responders were younger, more often female, and less likely to have comorbidities or a requirement for oxygen therapy, compared with nonresponders. At multivariate analysis, female sex (odds ratio [OR] 2.67; 95% confidence interval [CI] 1.29, 5.52; P = 0.0081), longer 6-minute walk distance (OR 1.01; 95% CI 1.00, 1.01; P = 0.0039), lower baseline log N-terminal-prohormone of brain natriuretic peptide (OR 0.70; 95% CI 0.52, 0.94; P = 0.0190), and aldosterone antagonist use (OR 2.54; 95% CI 1.03, 6.26; P = 0.0436) independently predicted response to initial combination therapy.

Besides demographic factors, the absence of comorbidities and less severe disease state, and the use of aldosterone antagonist therapy identified patients with PAH most likely to respond to initial combination therapy with ambrisentan and tadalafil. Further study to evaluate the role of aldosterone antagonist therapy in PAH is warranted.

Key words: Predictor analysis, Treatment responder, Phosphodiesterase type 5 inhibitor, Endothelin receptor antagonist, Aldosterone antagonist

Pulmonary arterial hypertension (PAH) is a progressive condition with several causes and is characterized by an increase in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR).1,2 Untreated PAH results in progressive right heart failure, with a median survival of 2.8 years.3,4 PAH therapies that target the endothelin, nitric oxide (NO) and prostacyclin pathways have resulted in significant improvements in survival, with advances in the last decade reflecting the combination of therapies that target multiple pathways.5,6

Initial combination therapy with ambrisentan (an endothelin receptor antagonist [ERA]) and tadalafil (a phosphodiesterase type 5 inhibitor [PDE5I]) resulted in a significantly lower risk of clinical failure events than with ambrisentan or tadalafil monotherapy in the large event-driven AMBITION study: the hazard ratio for first clinical failure event in combination therapy versus pooled monotherapy group was 0.50 (95% confidence interval [CI] 0.35, 0.72; P < 0.0001).5,6 In the latest European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, the initial concurrent use of ambrisentan and tadalafil is a recommended treatment strategy for low- and intermediate-risk patients.2 Although the prognosis of PAH has improved with the use of pulmonary vasodilators and initial combination therapy,5,7 PAH remains a life-limiting condition. There is a need for a greater understanding of patients most likely to benefit from initial combination therapy to inform long-term treatment approaches and patient counseling. Thus, to evaluate predic-
tors of response to initial combination therapy in treatment-naïve patients with PAH, we conducted an analysis of data from the AMBITION study.

Methods

Study design: This was a post hoc analysis of the AMBITION study, a multicenter, randomized, double-blind study to evaluate the usefulness of initial combination therapy with ambrisentan and tadalafil compared with either monotherapy in treatment-naïve patients with PAH, conducted between October 18, 2010, and July 31, 2014. Patients were randomized (2:1:1) to ambrisentan/tadalafil combination therapy, ambrisentan and placebo, or tadalafil and placebo, with the active treatments administered at an increasing dose (to a target of 10 mg for ambrisentan and 40 mg for tadalafil). The primary outcome of the AMBITION study was time to the first clinical failure event defined as the first occurrence of a composite endpoint of death, hospitalization for worsening PAH, disease progression (decrease of more than 15% from baseline in 6-minute walk distance [6MWD] combined with functional Class III or IV symptoms), or an unsatisfactory clinical response (any decline in a 6MWD from baseline and World Health Organization functional class [WHO-FC] III symptoms after 6 months on therapy). The protocol was approved by the institutional review board at each center. Details have been described previously.

Participants: Patients enrolled were aged 18-75 years and were treatment-naïve, and none were currently receiving ERA or PDE5I therapy. Patients had a diagnosis of idiopathic PAH, hereditary PAH, or PAH associated with drugs or toxins, connective tissue diseases, human immunodeficiency virus infection, or repaired congenital heart defects and had WHO-FC II or III symptoms. PAH was defined by the presence of mPAP ≥ 25 mmHg with a normal pulmonary artery wedge pressure (PAWP ≤ 15 mmHg) and PVR ≥ 240 dyne·seconds/cm². Eligibility criteria were refined following a blinded review after 6 months to include more rigorous hemodynamic requirements for PAH (mPAP ≥ 25 mm Hg with PVR ≥ 300 dyne·seconds/cm² and PAWP ≤ 12 mmHg [if PVR > 300 dyne·seconds/cm²] or ≤ 15 mm Hg [if PVR ≥ 500 dyne·seconds/cm²]). Additionally, patients with ≥ 3 risk factors for left ventricular diastolic dysfunction were excluded (body mass index ≥ 30 kg/m², history of essential hypertension, diabetes mellitus, or historical evidence of significant coronary artery disease [CAD]). The primary analysis set (PAS) in the AMBITION study included patients who met these refined criteria (n = 500). The present analysis was based on the combination therapy arm of the modified intention-to-treat (mITT) population to enhance the generalizability of the findings. The mITT population comprised all randomized patients who received ≥ 1 dose of study drug regardless of the amended entry criteria.

Statistical analysis: Analyses were based on responder and nonresponder populations within the combination therapy group, with responders (i.e., event-free subjects) defined as not having a clinical failure event. Univariate and multivariate analyses were performed to identify the baseline patient characteristics associated with response to combination therapy. Multivariate logistic regression analysis was used to determine the independent risk associated with each factor that showed a meaningful difference between cohorts, with the use of interactive backward selection to eliminate nonsignificant (P ≥ 0.10) covariates. Odds ratios (ORs), 95% CIs, and P-values are presented for the multivariate analysis. PAH etiology (PAH associated with connective tissue diseases [CTD-PAH] or non-CTD-PAH) and baseline WHO-FC II or III were kept in the multivariable model. Logarithm transformation was applied to baseline N-terminal-prohormone of brain natriuretic peptide (NT-proBNP) level for normalization.

Table I shows the covariates used in the univariate and multivariate analyses. The aldosterone antagonist diuretics were separated from the overall class of diuretics due to previous data showing a potentially significant benefit with spironolactone combined with ambrisentan. Comparisons between the responder and nonresponder populations were tested for statistical significance using the Mann-Whitney U test for continuous variables and the chi-square test for categorical data.

Results

Patients: The mITT population of the AMBITION study comprised 605 patients: 302 in the initial combination therapy group and 303 in the pooled monotherapy group. The mITT combination therapy group included 49 patients who had been excluded from the PAS (ex-PAS) because of risk factors for left ventricular diastolic dysfunction. Most patients in the combination therapy group were female (n = 223 [74%]), and the mean age was 55.9 ± 13.9 years. The most common PAH etiologies were idiopathic PAH (n = 156 [52%]) and CTD-PAH (n = 117 [39%]). Systemic sclerosis-associated PAH accounted for 81/117 (69%) patients with CTD-PAH. Mean ± standard deviation (SD) baseline 6MWD was 347.4 ± 91.77 m. In total, 69% of patients were categorized as WHO-FC III. Baseline hemodynamic data included mean ± SD mPAP 47 ± 13 mmHg, PAWP 9 ± 3 mmHg, cardiac index 2.5 ± 0.6 L/minute/m², and PVR 774 ± 456 dyne·seconds/cm².

Comparison of responders and nonresponders—univariate analysis: Among the 302 initial combination therapy patients, 234 subjects who did not have a clinical failure event were classed as responders and 68 subjects who had a clinical failure event were classed as nonresponders. Among the nonresponders, all failure events that occurred in the study were any-cause death (n = 27/68 [40%]), hospitalization for worsening PAH (n = 24/68 [35%]), disease progression (n = 19/68 [28%]), and inadequate clinical response (n = 25/68 [37%]).

The baseline variables that demonstrated a significant difference between groups were age, sex, race, CAD, ex-PAS status, oxygen therapy, WHO-FC, 6MWD, oxygen saturation, NT-proBNP, and Borg index (Table II). The mean ± SD age of responders and nonresponders was 54.4 ± 14.0 and 61.0 ± 12.2 years, respectively (P = 0.0003), and the proportion of females was 77% (n = 181) among the responder group compared with 62% (n =
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Table 1. Covariates Used in Multivariate Logistic Regression Analysis of the Clinical Response

| Covariate                                      | Entry item/unit |
|------------------------------------------------|-----------------|
| Age                                            | Years           |
| Sex                                            | Female, male    |
| Etiology of PAH                                 | CTD-PAH, non-CTD-PAH |
| WHO functional class (at baseline)             | II, III         |
| Body mass index (at baseline)                  | kg/m²           |
| Race                                           | White, non-white|
| Region                                         | North America, the rest of the world |
| Comorbidities                                  |                 |
| Diabetes mellitus                              | Yes, No         |
| Hypertension                                   | Yes, No         |
| Coronary artery disease                        | Yes, No         |
| Population                                     | PAS, Ex-PAS     |
| Prior medications:                             |                 |
| Oxygen                                         | Yes, No         |
| Anticoagulants                                 | Yes, No         |
| Calcium channel blockers                       | Yes, No         |
| Diuretics (excluding aldosterone antagonists)  | Yes, No         |
| Aldosterone antagonist diuretics               | Yes, No         |
| Hemodynamic variables at baseline              |                 |
| Mean pulmonary arterial pressure               | mmHg            |
| Pulmonary vascular resistance                  | dynes-seconds/cm² |
| Pulmonary capillary wedge pressure             | mmHg            |
| Cardiac index                                  | L/minute/m²     |
| Log NT-proBNP (at baseline)                    | ng/L            |
| 6-minute walk distance (at baseline)           | meters          |
| Borg score (at baseline)                       | –               |
| FEV₁ (at baseline)                             | % predicted     |
| TLC (at baseline)                              | % predicted     |
| Oxygen in the blood (at baseline)              | %               |

CTD indicates connective tissue disease; ex-PAS, excluded from primary analysis set; FEV₁, forced expiratory volume in one second; NT-proBNP, N-terminal-prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAS, primary analysis set; TLC, total lung capacity; and WHO, World Health Organization.

42) among nonresponders (P = 0.0100). Compared with the nonresponder group, the responder group had a lower proportion of CAD (% versus 16%, P = 0.0257), a lower proportion of ex-PAS patients (14% versus 25%, P = 0.0258), lower use of oxygen therapy (23% versus 41%, P = 0.0031), higher proportion of WHO-FC II (36% versus 13%, P = 0.0004), longer baseline 6MWD (mean ± SD: 359.7 m ± 89.6 versus 305.2 m ± 85.3, P < 0.0001), lower baseline NT-proBNP (mean ± SD: 601.8 ng/L ± 1473.7 versus 1212.0 ng/L ± 2192.3, P = 0.0010), and higher oxygen saturation (mean ± SD: 95.5% ± 2.9 versus 94.4% ± 2.6, P = 0.0019) (Table II). The Borg score in the responder group was lower than that observed in the nonresponder group (mean ± SD: 4.2 ± 2.3 versus 5.3 ± 2.4, P = 0.0014). However, there was no significant difference between the groups in mean ± SD forced expiratory volume in one second (FEV₁) percent predicted (responders 84.9 ± 17.1; nonresponders 85.3 ± 19.0, P = 0.9541) or total lung capacity (TLC) percent predicted (responders 93.1 ± 15.1; nonresponders 92.1 ± 17.2; P = 0.5894).

Predictors of response—multivariate analysis: Results of the multivariate logistic regression analysis are shown in the Figure. The following were identified as independent predictors of response to initial combination therapy: female sex (OR 2.669 [95% CI 1.291, 5.518], P = 0.0081), use of aldosterone antagonist diuretics (OR 2.535 [95% CI 1.027, 6.257], P = 0.0436), lower baseline log NT-proBNP (OR 0.704 [95% CI 0.524, 0.944], P = 0.0190), and longer baseline 6MWD (OR 1.006 [95% CI 1.002, 1.010], P = 0.0039). As a reference, independent predictors of response to monotherapy included coexisting diabetes mellitus, use of calcium channel blockers, lower baseline mPAP mmHg, lower baseline log NT-proBNP, and longer baseline 6MWD (data not shown).

Discussion

In this post hoc analysis of the AMBITION study, we have shown that patients with PAH who respond to initial combination therapy tend to be younger and female, have fewer cardiovascular comorbidities, are less likely to have used oxygen therapy, and have a physiologically less severe disease (with lower NT-proBNP, longer 6MWD, low Borg index, high oxygen saturation, and WHO-FC II). Additionally, the use of aldosterone antagonist therapy was associated with treatment response. However, whether routine use of aldosterone antagonist therapy should be recommended in patients with PAH requires further evaluation. A number of our results are corroborated by previously published data.11,12) Disease severity, demographics,
## Table II. Baseline Demographic, Functional, and Hemodynamic Status of Responders and Nonresponders to Initial Combination Therapy (mITT Population)

| Variable | Total combination therapy | Responder | Nonresponder | $P$-value (responder versus nonresponder) |
|----------|---------------------------|-----------|--------------|----------------------------------------|
|          | $n$                       | 302       | 234          | 68                                     | –                                      |
| Age, years | 55.9 (13.9)               | 54.4 (14.0) | 61.0 (12.2) | 0.0003*                                 |
| Female    | 223 (74%)                 | 181 (77%) | 42 (62%)     | 0.0100                                  |
| Body mass index | 28.9 (7.0) | 28.8 (7.3) | 29.0 (6.3) | 0.5824*                                 |
| Race–White | 281 (93%)                 | 214 (91%) | 67 (99%)     | 0.0434                                  |
| Region–North America | 135 (45%) | 107 (46%) | 28 (41%)     | 0.5065                                  |
| Comorbidity |                      |           |              |                                         |
| Hypertension | 146 (48%)                | 107 (46%) | 39 (57%)     | 0.0913                                  |
| Diabetes   | 50 (17%)                  | 36 (15%)  | 14 (21%)     | 0.3095                                  |
| CAD       | 28 (9%)                   | 17 (7%)   | 11 (16%)     | 0.0257                                  |
| Ex-PAS population | 49 (16%)  | 32 (14%)  | 17 (25%)     | 0.0258                                  |
| Etiology of PAH |              |           |              |                                         |
| Idiopathic | 156 (52%)                | 119 (51%) | 37 (54%)     | 0.4221                                  |
| Heritable  | 10 (3%)                   | 9 (4%)    | 1 (1%)       |                                         |
| Associated with CTD | 117 (39%) | 88 (38%)  | 29 (43%)     |                                         |
| Associated with CHD | 5 (2%)   | 5 (2%)    | 0            |                                         |
| Associated with HIV infection | 5 (2%)  | 5 (2%)    | 0            |                                         |
| Associated with drug use or toxin exposure | 9 (3%)   | 8 (3%)    | 1 (1%)       |                                         |
| Presence of CTD-PAH | 117 (39%) | 88 (38%)  | 29 (43%)     | 0.4527                                  |
| Presence of SSc-PAH | 81 (27%)   | 60 (26%)  | 21 (31%)     | 0.3905                                  |
| Prior medications |                      |           |              |                                         |
| Oxygen therapy | 82 (27%)                 | 54 (23%)  | 28 (41%)     | 0.0031                                  |
| Anticoagulants | 89 (29%)                  | 72 (31%)  | 17 (25%)     | 0.3583                                  |
| Calcium channel blocker | 82 (27%) | 64 (27%)  | 18 (26%)     | 0.8858                                  |
| Diuretics excluding aldosterone antagonist | 161 (53%) | 120 (51%) | 41 (60%)     | 0.1898                                  |
| Aldosterone antagonist | 59 (20%)             | 48 (21%)  | 11 (16%)     | 0.4273                                  |
| WHO functional class |              |           |              |                                         |
| II         | 93 (31%)                  | 84 (36%)  | 9 (13%)      | 0.0004                                  |
| III        | 209 (69%)                 | 150 (64%) | 59 (87%)     |                                         |
| 6MWD, meters | 347.4 (91.7)             | 359.7 (89.6) | 305.2 (85.3) | < 0.0001*                               |
| FEV1, % predicted | 83.3 (17.9)               | 84.9 (17.1) | 85.3 (19.0) | 0.9541*                                  |
| TLC, % predicted | 90.7 (18.0) $n = 301$  | 93.1 (15.1) $n = 234$ | 92.1 (17.2) $n = 67$ | 0.5894*                                  |
| Oxygen level in blood, % | 95.3 (3.2)      | 95.5 (2.9) | 94.4 (2.6) | 0.0019*                                  |
| mPAP, mm Hg | 47 (13)                   | 47.2 (13.2) | 46.9 (9.8) | 0.8074*                                  |
| PAWP, mm Hg | 9 (3) $n = 291$           | 8.8 (3.1) $n = 227$ | 9.0 (3.6) $n = 64$ | 0.5635*                                  |
| Cardiac index, L/minute/m² | 2.5 (0.6) $n = 298$ | 2.4 (0.6) $n = 230$ | 2.5 (0.7) $n = 68$ | 0.8206*                                  |
| PVR, dyne-seconds/cm⁵ | 774 (456)               | 769.2 (416.6) | 790.3 (575.1) | 0.9767*                                  |
| NT-proBNP, ng/L¹ | 1486.4 (1692.5)         | 601.8 (1473.7) | 1212.0 (2192.3) | 0.0010*                                  |
| Borg score | 4.5 (2.4) $n = 301$ | 4.2 (2.3) $n = 233$ | 5.3 (2.4) $n = 68$ | 0.0014*                                  |
| Event     |                          |           |              |                                         |
| Event of clinical failure | 68 (23%)     | 0         | 68 (100%)    |                                         |
| Clinical worsening event | 55 (18%)     | 0         | 55 (81%)     |                                         |
| Death from any cause | 27 (9%)       | 0         | 27 (40%)     |                                         |
| Hospitalization for worsening PAH | 24 (8%) | 0         | 24 (35%)    |                                         |
| Disease progression | 19 (6%)       | 0         | 19 (28%)     |                                         |
| Unsatisfactory long-term clinical response | 25 (8%) | 0         | 25 (37%)    |                                         |

Data are mean (standard deviation) or number (percent). In cases of missing values, the numbers of patients are given. Statistical comparison was conducted using the Chi-square test unless noted. *Statistical comparison conducted using the Mann–Whitney U test; †geometric mean is used for NT-proBNP. CAD indicates coronary artery disease; CHD, congenital heart disease; CTD, connective tissue disease; ex-PAS, excluded from the primary analysis set; FEV1, forced expiratory volume in one second; HIV, human immunodeficiency virus; mITT, modified intent-to-treat; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal-prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SSc-PAH, systemic sclerosis-associated PAH; TLC, total lung capacity; WHO, World Health Organization; and 6MWD, 6-minute walk distance.

and the presence or absence of comorbidities are all known to have an impact on PAH prognosis, and it is perhaps not surprising that these factors also predict patients most likely to respond to initial combination oral therapy. In this study, baseline NT-proBNP level and 6MWD, which are recommended risk assessment measures in the ESC/ERS PAH guidelines,²¹ independently predicted treatment response in our multivariate regression analysis.
Our analysis also identified sex as a predictor of response to initial combination therapy, which was not the case for monotherapy. This observation is consistent with patient-level data analysis from six randomized placebo-controlled trials of ERAs showing that female patients with PAH had greater responses to ERAs (i.e., ambrisentan and macitentan) than male patients. However, because idiopathic PAH is associated with female sex in epidemiological studies and females accounted for 74% of the mITT combination therapy group, in the AMBITION study, further analysis may be needed to clarify the association. Of note, female sex was also identified as an independent factor for treatment response in a multivariate logistic regression analysis of the full mITT population (OR 1.687; 95% CI 1.010, 2.819; \( P = 0.0458; n = 605; \) data not shown).

A further finding was the association of the use of aldosterone antagonist therapy as an independent predictor of treatment response, although no significant differences were noted in the proportion of patients receiving aldosterone antagonists in the responder and nonresponder groups. Mineralocorticoid receptor antagonism attenuates experimental pulmonary hypertension in animal models, and its use with endothelin type-A receptor antagonists may be clinically beneficial in PAH because of a potentially synergistic mechanism of action. Progression of PAH is affected by systemic alterations including upregulation of the renin-angiotensin-aldosterone system and dysfunction of the metabolic pathway. Aldosterone is a vasoactive substance that stimulates the mineralocorticoid receptor in the pulmonary endothelial cells to induce hypertrophic and fibrotic pulmonary arterial remodeling in PAH and a decrease in cardiac output. This in turn upregulates the renin-angiotensin-aldosterone system, which is independently associated with cardiovascular remodeling via an increase in circulating aldosterone. Furthermore, this increase in aldosterone stimulates the mineralocorticoid receptor and leads to a decrease in bioavailable NO via modification of the endothelial nitric oxide synthase activating region of the endothelial endothelin-B (ETB) receptor by increasing the accumulation of reactive oxygen species in pulmonary artery endothelial cells. Also, metabolic dysfunction characterized by atypical PAH (i.e., the ex-PAS-type population) may explain the decrease in NO synthesis in endothelial cells isolated from patients with idiopathic PAH. Thus, the combination of ambrisentan and spironolactone may contribute to the preservation of ETB-dependent vasodilatation, with an expected synergistic effect on bioavailable NO by maintaining endothelial ETB function that is needed for the efficacy of the PDE5I. Diuretics are generally used in PAH management because right-sided heart failure causes fluid retention, with the utilization of loop diuretics, thiazide diuretics, and aldosterone antagonists, as monotherapy or in combination. Now that the mechanism of PAH progression involving these factors has been highlighted, further investigation is warranted to elucidate specific and synergistic effects of ambrisentan with spironolactone.

The ex-PAS patients, who had multiple risk factors for left ventricular diastolic dysfunction, were overrepresented in the nonresponder group compared with the responder group. The ex-PAS population represents an older subgroup of patients with PAH and cardiovascular comorbidities, where heart failure with preserved ejection fraction is common and is a recognized adverse prognostic factor. Mean baseline values of FEV₁ and TLC were high (83.3% and 90.7% predicted, respectively, in the total combination therapy group) and did not differ significantly between the responder and nonresponder groups. This may reflect the study inclusion criteria of FEV₁ ≥ 55% and TLC ≥ 60% of predicted normal (within 24 weeks of screening). The responder and nonresponder groups also did not appear to differ overall in the severity of baseline pulmonary hemodynamic parameters. A possi-
able explanation for this is that the nonresponder group would have included comorbid patients with milder hemodynamic parameters as well as patients with more severe disease who would be expected to deteriorate.

This analysis has some limitations. As it was post hoc, it was limited by the available data. As only all-cause mortality data were available, the proportion of deaths that were not related to PAH could not be determined. Other limitations in data availability included the lack of patient-level data; for example, as data on patient characteristics in those who received aldosterone antagonists were unavailable, potential differences in patient background with or without aldosterone antagonist administration could not be assessed. Further interpretation of the lack of difference between responders and nonresponders in baseline hemodynamic parameters would have been possible if mean right arterial pressure and mixed venous oxygen saturation data were available. An analysis of whether differing capacity for carbon monoxide predicted clinical response would also have been of value; unfortunately, these data were also not available for analysis. Finally, only baseline parameter values were assessed in this analysis; it was not possible to examine the impact of the intervention on variables, including hemodynamics, as they were not measured repeatedly in the AMBITION study.

The AMBITION study established initial combination therapy as the standard of care for patients with PAH in low- and intermediate-risk groups. The current findings highlight that those patients who are younger, female, and with fewer comorbidities and less severe physiological disease are most likely to respond to initial combination therapy with ambrisentan and tadalafil. The use of aldosterone antagonist therapy was associated with treatment response. Further studies to evaluate the potential benefits of aldosterone antagonist therapy in PAH are warranted.

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Disclosure

Conflicts of interest: MH works in a department endowed by Actelion Pharmaceuticals Japan, Nippon Shinyaku Co. Ltd, and Mochida Pharmaceutical Co. Ltd. and has received personal fees from Bayer Yakuhin Ltd, Actelion Pharmaceuticals Japan, Pfizer Japan Inc., and Nippon Shinyaku Co. Ltd. KA has received consulting fees from Actelion Pharmaceuticals Japan and a research grant from Mochida Pharmaceutical Co. Ltd. GK declares no competing interests. TT is a former employee of GSK. GT is an employee of GSK and holds GSK stocks/shares. DGK has received consulting fees and funding to attend educational meetings from Actelion, Bayer, GSK, and MSD, and his department has received grant funding from Actelion and GSK.

Author contributions: MH, GT, and TT conceived of the analysis. MH, KA, GK, and DGK were involved in data acquisition in the AMBITION study. TT and GK performed the current analysis. All authors contributed to data interpretation. All authors revised the manuscript critically for important intellectual content, approved the final version for publication, and agreed to be listed as authors.

Declarations: Ethics approval and informed consent to participate. The protocol was approved by the Institutional Review Boards and/or Independent Ethics Committees at each center. Details have been described previously.1-3,7,8,10

Trial registration: NCT01178073; A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension (PAH) (AMBITION); https://www.clinicaltrials.gov/ct2/show/NCT01178073?term=NCT01178073&draw=2&rank=1

Data availability: Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com or should be directed to the corresponding author.

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