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Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial

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KEYWORDS:
ambrisentan;
tadalafil;
combination therapy;
pulmonary arterial hypertension;
randomized controlled trial

BACKGROUND: The purpose of this study was to compare patients with pulmonary arterial hypertension enrolled in the AMBITION trial with (excluded from the primary analysis set [ex-primary analysis set]) and without (primary analysis set) multiple risk factors for left ventricular diastolic dysfunction.

METHODS: Treatment-naive patients with pulmonary arterial hypertension were randomized to once-daily ambrisentan and tadalafil combination therapy, ambrisentan monotherapy, or tadalafil monotherapy. The primary end point was time from randomization to first adjudicated clinical failure event.

RESULTS: Primary analysis set patients ($n = 500$), compared with ex-primary analysis set patients ($n = 105$), were younger (mean, 54.4 vs 62.1 years) with greater baseline 6-minute walk distance (median, 363.7 vs 330.5 meters) and fewer comorbidities (e.g., hypertension and diabetes). Treatment effects of initial combination therapy vs pooled monotherapy were directionally the same for both populations, albeit of a lower magnitude for ex-primary analysis set patients. Initial combination therapy reduced the risk of clinical failure compared with pooled monotherapy in primary analysis set patients (hazard ratio, 0.50; 95% confidence interval, 0.35—0.72), whereas the effect was less clear in ex-primary

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analysis set patients (hazard ratio, 0.70; 95% confidence interval, 0.35−1.37). Overall, primary analysis set patients had fewer clinical failure events (25% vs 33%), higher rates of satisfactory clinical response (34% vs 24%), and lower rates of permanent study drug withdrawal due to adverse events (16% vs 31%) than ex-primary analysis set patients.

CONCLUSIONS: Efficacy of initial combination therapy vs pooled monotherapy was directionally similar for primary analysis set and ex-primary analysis set patients. However, ex-primary analysis set patients (with multiple risk factors for left ventricular diastolic dysfunction) experienced higher rates of clinical failure events and the response to combination therapy vs monotherapy was attenuated. Tolerability was better in primary analysis set than ex-primary analysis set patients.

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Registry data indicate that the demographics of patients with pulmonary arterial hypertension (PAH) have changed over time.[1−7] At least in Western countries, the proportion of patients being diagnosed at a more advanced age and/or with more risk factors for left ventricular diastolic dysfunction is increasing.[8,9] Clinical outcomes are worse in such patients relative to their younger counterparts who have fewer risk factors for left ventricular diastolic dysfunction.[8,9] These observations have led to some uncertainty in how best to categorize and treat these patients based on the current clinical classification of pulmonary hypertension.[10−13] Traditionally, patients with advanced age and/or risk factors for left ventricular diastolic dysfunction have largely been excluded from clinical trials with PAH medications. Hence, the safety and efficacy of PAH treatments are not well established in such patients. Therefore, clinicians are increasingly encountering patients in whom the classification of pulmonary hypertension is challenging and for whom there is limited evidence to guide treatment decisions.

The AMBITION trial was performed in patients with treatment-naive PAH. A blinded clinical end point committee reviewed demographic data within the first 6 months of study initiation and found a higher than expected prevalence of risk factors for left ventricular diastolic dysfunction. Despite meeting the hemodynamic criteria for PAH,[10,11] the risk factors raised concern that the study was recruiting a high proportion of patients in whom the treatments had not been well established previously and in whom the diagnosis of group 1 PAH may be more difficult to establish. The end point committee also noted that, for some patients, the hemodynamics obtained during right heart catheterization were only minimally abnormal (e.g., mean pulmonary arterial pressure only slightly above 25 mm Hg and pulmonary vascular resistance only slightly above 3 Wood units). To reduce the likelihood of further enrolling patients in whom left ventricular diastolic dysfunction may have been a contributing factor to their pulmonary hypertension, the steering committee recommended amending the eligibility criteria by setting more stringent hemodynamic requirements, requiring a higher pulmonary vascular resistance if the left ventricular end-diastolic pressure or pulmonary capillary wedge pressure was close to the upper limit of the allowed cutoff (12−15 mm Hg), and excluding patients with more than 2 risk factors for left ventricular diastolic dysfunction. Risk factors included body mass index ≥30 kg/m^2, history of essential hypertension, diabetes mellitus, or historical evidence of significant coronary disease. The amendment became effective after 14 to 18 months of enrollment.

Therefore, the AMBITION trial included patients who met the amended eligibility criteria (termed primary analysis set patients in the trial) and those who did not (termed ex-primary analysis set patients in the trial). The latter group represented a well-characterized cohort that met the accepted definition of PAH but had multiple cardiovascular risk factors for left ventricular diastolic dysfunction and/or modest hemodynamic derangements.[14] In the absence of universally accepted definitions or terms to describe these patients, and to remain consistent with the terminology used in the primary paper,[14] herein we use the terms *primary analysis set* and *ex-primary analysis set* when referring to methods and results from the AMBITION trial. This pre-specified additional analysis of the AMBITION trial compared the characteristics and outcomes seen in primary analysis set patients with those seen in ex-primary analysis set patients.

Methods

Patients

Methods were described previously.[14] Briefly, treatment-naive patients aged 18 to 75 years and diagnosed with idiopathic or hereditary PAH or PAH associated with connective-tissue disease, drugs or toxins, human immunodeficiency virus (stable disease), or repaired congenital heart defects with World Health Organization (WHO) functional class II or III symptoms were included. The initial and revised eligibility criteria based on the protocol amendment are shown in Table 1. Ex-primary analysis set patients either (1) had pulmonary vascular resistance of 3 to 3.75 Wood units, (2) had pulmonary vascular resistance of 3.75 to 6.25 Wood units and pulmonary capillary wedge pressure of 13 to 15 mm Hg, (3) had more than 2 risk factors for left ventricular diastolic dysfunction, or (4) failed the initial protocol criteria of confirmed diagnosis of PAH after randomization into the study. All patients provided written informed consent. The protocol was approved by Institutional Review Boards and/or Independent Ethics Committees, and the study was conducted in accordance with ethical principles of the Declaration of Helsinki.

Study design

In this double-blind study, patients were stratified by PAH etiology (idiopathic or hereditary vs non-idiopathic) and WHO

Table 1 Changes in Eligibility Criteria Based on Protocol Amendment

Initial protocol	Revised criteria
Inclusion criteria:	*Inclusion criteria:*
Confirmed diagnosis of PAH with[a]:	Confirmed diagnosis of PAH with[a]:
- mPAP ≥25 mm Hg	- mPAP ≥25 mm Hg
- PVR ≥240 dyne•sec/cm^5	- PVR ≥300 dyne•sec/cm^5
- PCWP or LVEDP ≤15 mm Hg	- PCWP or LVEDP ≤12 mm Hg if PVR ≥300 to <500 dyne•sec/cm^5
Exclusion criteria:	- or PCWP or LVEDP ≤15 mm Hg if PVR ≥500 dyne•sec/cm^5
No exclusions with regard to cardiovascular risk factors	*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, or stable angina

Abbreviations: 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.

[a]Based on right heart catheterization before screening.

Table was included in the Supplementary Appendix (Table S2) of the primary paper. From *N Engl J Med*, Galiè N, Barberà JA, Frost AE, et al, Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension, 2015, Volume No. 373, Page No. 834-44, Copyright (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

functional class (II vs III) and randomized 2:1:1 to receive once-daily combination therapy with ambrisentan and tadalafil, monotherapy with ambrisentan, or monotherapy with tadalafil, respectively. Ambrisentan was titrated to a 10-mg target dose, and tadalafil was titrated to a 40-mg target dose.

Study assessments

Efficacy and safety assessments were made at screening; randomization; Weeks 4, 8, 16, and 24; every 12 weeks thereafter; and at the final assessment and end-of-study visits. The primary end point was time from randomization to first adjudicated clinical failure event, defined as the first occurrence of a composite of the following: (1) death; (2) hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart and/or lung transplant, atrial septostomy, or initiation of parenteral prostanoid therapy); (3) disease progression (>15% reduction from baseline in 6-minute walk distance [6MWD] plus WHO functional class III or IV symptoms at 2 consecutive visits separated by ≥14 days); or (4) unsatisfactory long-term clinical response (any reduction from baseline in 6MWD at 2 consecutive post-baseline visits separated by ≥14 days and WHO functional class III symptoms assessed at 2 clinic visits separated by ≥6 months). All reported clinical failure events were adjudicated by an independent clinical end point committee that was blinded to treatment assignment and investigator.

Secondary end points evaluated at Week 24 included the change from baseline in N-terminal probrain natriuretic peptide (NT-proBNP) level, satisfactory clinical response, change from baseline in 6MWD, WHO functional class, and Borg dyspnea index. A satisfactory clinical response was defined as a ≥10% increase from baseline in 6MWD, with a reduction to (or maintenance of) WHO functional class I or II symptoms and no events of clinical worsening before or at the Week 24 visit. All reported or observed adverse events (AEs) were recorded during the study. Laboratory safety assessments were performed monthly. A follow-up safety assessment was performed by telephone 30 days after administration of the last dose of study medication.

Statistical analyses

Statistical methods for primary analysis set patients were described previously.[14] Inferential statistical analysis was not planned for ex-primary analysis set patients because of the small sample size. The Kaplan−Meier product limit method was used to generate survival curves for the primary end point. Secondary end points were analyzed using descriptive statistics. For NT-proBNP levels and the percentage of patients with satisfactory clinical response, there was no imputation for missing values. For 6MWD, missing values were imputed using the last observation carried forward or, in the event of missing data following death or hospitalization for PAH, worst rank scores. Post-hoc analyses included calculation of the hazard ratio (HR) and 95% confidence interval (CI) for time from randomization to first adjudicated clinical failure event from a Cox proportional-hazards regression model, and calculation of 95% CIs for median 6MWD and mean NT-proBNP. Statistical analyses were performed by Hartington Statistics and Data Management Ltd (London, United Kingdom) and PharPoint Research (Durham, NC) and were overseen by the sponsors.

Results

Patients

Of 610 randomized patients, 5 did not receive study medication. Of the remaining randomized and treated patients, 500 were primary analysis set patients and 105 were ex-primary analysis set patients. Disposition for both groups was reported previously.[14]

Among 105 ex-primary analysis set patients, 9 did not meet the amended hemodynamic criteria and had more than 2 cardiovascular risk factors; 54 met the amended hemodynamic criteria but had more than 2 cardiovascular risk factors; 39 did not meet the amended hemodynamic criteria but had fewer than 3 cardiovascular risk factors, including 1 patient who had a pulmonary vascular resistance of <3 Wood units; and 3 met the amended hemodynamic criteria and had fewer than 3 cardiovascular risk factors but were rediagnosed as not having PAH during the study.

At baseline, primary analysis set patients, compared with ex-primary analysis set patients, were on average younger with greater median 6MWD and lower incidences of hypertension, diabetes mellitus, and coronary artery disease (Table 2). Primary analysis set patients also had greater mean pulmonary arterial pressure and mean pulmonary vascular resistance and lower mean pulmonary capillary wedge pressure (Table 2).

Treatment efficacy: Primary analysis set and ex-primary analysis set

In primary analysis set patients, initial combination therapy was associated with a 50% reduction in risk of clinical failure compared with pooled monotherapy (HR, 0.50; 95% CI, 0.35−0.72; $p < 0.001$; Figure 1a). In ex-primary analysis set patients, initial combination therapy was associated with a 30% reduction in risk of clinical failure compared with pooled monotherapy (HR, 0.70; 95% CI, 0.35−1.37; Figure 1b).

Table 2 Demographic and Baseline Characteristics in Primary Analysis Set and Ex-Primary Analysis Set Patients

	Primary analysis set			Ex-primary analysis set		
Characteristic	Combination therapy (*n* = 253)	Pooled monotherapy (*n* = 247)	Total (*N* = 500)	Combination therapy (*n* = 49)	Pooled monotherapy (*n* = 56)	Total (*N* = 105)
Age, years	54.5 (14.3)	54.2 (14.9)	54.4 (14.6)	62.8 (8.7)	61.5 (11.3)	62.1 (10.2)
Female, *n* (%)	188 (74)	200 (81)	388 (78)	35 (71)	38 (68)	73 (70)
Region, *n* (%)						
North America	116 (46)	112 (45)	228 (46)	19 (39)	27 (48)	46 (44)
Rest of world	137 (54)	135 (55)	272 (54)	30 (61)	29 (52)	59 (56)
Etiology of PAH, *n* (%)					(*n* = 55)	(*n* = 104)
iPAH	127 (50)	138 (56)	265 (53)	29 (59)	36 (65)	65 (63)
hPAH	7 (3)	7 (3)	14 (3)	3 (6)	0	3 (3)
Associated PAH	119 (47)	102 (41)	221 (44)	17 (35)	19 (35)	36 (35)
WHO functional class, *n* (%)						
II	76 (30)	79 (32)	155 (31)	17 (35)	20 (36)	37 (35)
III	177 (70)	168 (68)	345 (69)	32 (65)	36 (64)	68 (65)
NT-proBNP, ng/liter						
n	236	235	471	47	54	101
Median	938.0	1,018.0	1,004.0	400.0	477.4	454.0
IQR	328.0−2,484.5	334.0−1,889.0	332.0−2,096.0	188.0−1,226.0	174.0−1,777.0	184.0−1,396.0
6MWD, meters						
Mean (SD)	353.5 (87.9)	351.7 (91.8)	352.6 (89.8)	316.1 (103.2)	323.9 (95.0)	320.3 (98.5)
Median	357.0	365.5	363.7	333.0	329.1	330.5
IQR	292.0−425.3	297.5−425.2	295.3−425.2	220.2−409.5	249.2−394.5	245.5−404.5
Comorbidities						
Hypertension, *n* (%)	104 (41)	95 (38)	199 (40)	42 (86)	39 (70)	81 (77)
Diabetes mellitus, *n* (%)	19 (8)	30 (12)	49 (10)	31 (63)	28 (50)	59 (56)
CAD, *n* (%)	16 (6)	4 (2)	20 (4)	12 (24)	10 (18)	22 (21)
Hemodynamics						
mRAP, mm Hg	7.7 (4.5) (*n* = 252)	7.9 (4.7) (*n* = 246)	7.8 (4.6) (*n* = 498)	8.6 (3.9) (*n* = 47)	9.1 (4.8)	8.9 (4.4) (*n* = 103)
Cardiac index, liters/min/m^2	2.4 (0.6) (*n* = 249)	2.4 (0.7) (*n* = 243)	2.4 (0.7) (*n* = 492)	2.6 (0.6)	2.6 (0.6) (*n* = 55)	2.6 (0.6) (*n* = 104)
mPAP, mm Hg	48.1 (12.4)	49.3 (12.6)	48.7 (12.5)	42.4 (12.0)	42.0 (12.9)	42.2 (12.4)
PCWP, mm Hg	8.4 (3.1) (*n* = 244)	8.9 (3.4) (*n* = 236)	8.7 (3.2) (*n* = 480)	11.0 (3.2) (*n* = 47)	11.6 (3.8) (*n* = 55)	11.3 (3.5) (*n* = 102)
PVR, dyne•sec/cm^5	824.1 (467.0)	825.7 (402.1)	824.9 (435.7)	515.0 (278.4)	509.5 (308.1)	512.1 (293.2)

Abbreviations: 6MWD, 6-minute walk distance; CAD, coronary artery disease; hPAH, heritable pulmonary arterial hypertension; iPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.

Values are mean (SD) unless otherwise stated.

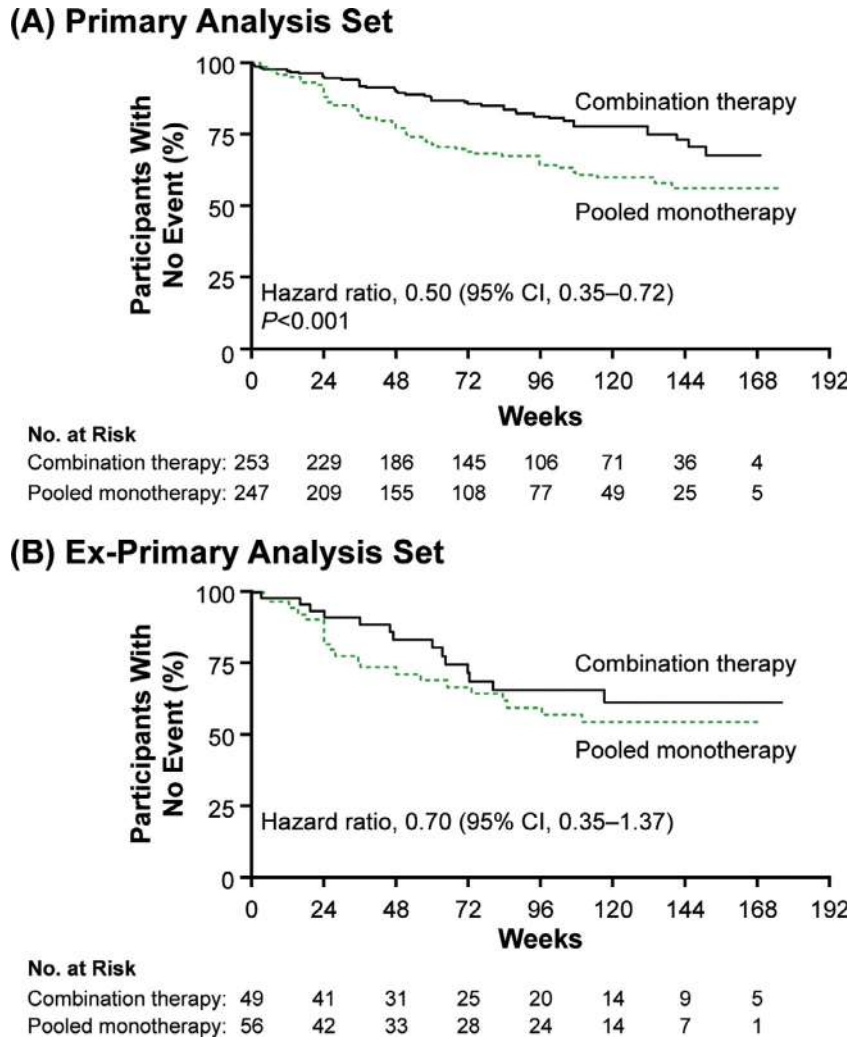

Figure 1 Kaplan-Meier curves for the primary end point of time from randomization to first clinical failure event. (**A**) Primary analysis set patients and (**B**) ex-primary analysis set patients. Statistical significance testing was not performed for ex-primary analysis set patients because of the relatively small sample size. Ex-primary analysis set is a post-hoc figure. Panel A from *N Engl J Med*, Galiè N, Barberà JA, Frost AE, et al, Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension, 2015, Volume No. 373, Page No. 834-44, Copyright (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. CI, confidence interval.

In both primary analysis set and ex-primary analysis set patients, the treatment effect was driven mainly by a lower rate of hospitalization for worsening PAH in the initial combination therapy arm (Table 3). Among primary analysis set patients, 10 (4%) had hospitalization for worsening PAH as the first clinical failure event with initial combination therapy compared with 30 (12%) with pooled monotherapy. Considering all hospitalizations for worsening PAH (either as first or subsequent clinical failure event), the number of primary analysis set patients with at least 1 hospitalization for worsening PAH was 19 (8%) vs 44 (18%), respectively, and the total number of hospitalizations for worsening PAH was 25 vs 53, respectively, for combination vs pooled monotherapy.

Among ex-primary analysis set patients, 1 (2%) had hospitalization for worsening PAH as the first clinical failure event with initial combination therapy vs 6 (11%) with pooled monotherapy. Considering all hospitalizations for worsening PAH (either as first or subsequent clinical failure event), the number of ex-primary analysis set patients with at least 1 hospitalization for worsening PAH was 5 (10%) for combination therapy vs 13 (23%) for pooled monotherapy, and the total number of hospitalizations for worsening PAH was 6 for combination therapy vs 17 for pooled monotherapy.

Changes from baseline at Week 24 in NT-proBNP levels and 6MWD are shown in Figure 2 and Figure 3, respectively. In primary analysis set patients, initial combination therapy provided a statistically significantly ($p < 0.001$) greater benefit than pooled monotherapy to NT-proBNP levels (change in geometric mean: −67.2% vs −50.4%) and 6MWD (median change: +49.0 meters vs +23.8 meters). For ex-primary analysis set patients, the changes were −32.7% (95% CI, −49.5% to −10.3%) vs −19.1% (95% CI, −39.4% to 7.8%) for NT-proBNP levels and +19.6 meters (95% CI, 6.7−43.0 meters) vs + 11.4 meters (95% CI, −8.3 to 26.0 meters) for 6MWD.

Primary analysis set patients receiving initial combination therapy had a higher rate of satisfactory clinical response compared with those receiving pooled monotherapy (39% vs

Table 3 Summary of First Clinical Failure Event in Primary Analysis Set and Ex-Primary Analysis Set Patients

	Primary analysis set			Ex-primary analysis set		
First event	Combination therapy ($n = 253$)	Pooled monotherapy ($n = 247$)	Total ($N = 500$)	Combination therapy ($n = 49$)	Pooled monotherapy ($n = 56$)	Total ($N = 105$)
Patients with a first event, n (%)	46 (18)	77 (31)	123 (25)	14 (29)	21 (38)	35 (33)
Death	9 (4)	8 (3)	17 (3)	4 (8)	4 (7)	8 (8)
Hospitalization for worsening PAH	10 (4)	30 (12)	40 (8)	1 (2)	6 (11)	7 (7)
Disease progression	10 (4)	16 (6)	26 (5)	5 (10)	5 (9)	10 (10)
Unsatisfactory long-term clinical response	17 (7)	23 (9)	40 (8)	4 (8)	6 (11)	10 (10)

Abbreviation: PAH, pulmonary arterial hypertension.

29%; odds ratio, 1.563; 95% CI, 1.054−2.319; $p = 0.03$) than ex-primary analysis set patients (26% vs 22%, respectively).

Treatment efficacy: Primary analysis set vs ex-primary analysis set

The overall percentage of patients with a first clinical failure event was lower in primary analysis set vs ex-primary analysis set patients (25% vs 33%), primarily resulting from a lower rate of disease progression (5% vs 10%) and death (3% vs 8%) (Table 3).

At Week 24, compared with baseline, greater reductions in NT-proBNP levels (Figure 2) and increases in 6MWD (Figure 3) were observed in primary analysis set than ex-primary analysis set patients.

The rate of satisfactory clinical response at Week 24 for the entire AMBITION cohort was greater for primary analysis set than ex-primary analysis set patients (34% vs 24%).

Safety

The types of AEs reported were similar between primary analysis set and ex-primary analysis set patients (Table 4). The most common AE was peripheral edema. Among AEs reported in >10% of patients in any treatment group, the following were more common (>5% difference) with initial combination therapy than with either monotherapy in primary analysis set patients but not in ex-primary analysis set patients: headache, nasal congestion, dizziness, anemia, and bronchitis. The following AEs were more common (>5% difference) with initial combination therapy than

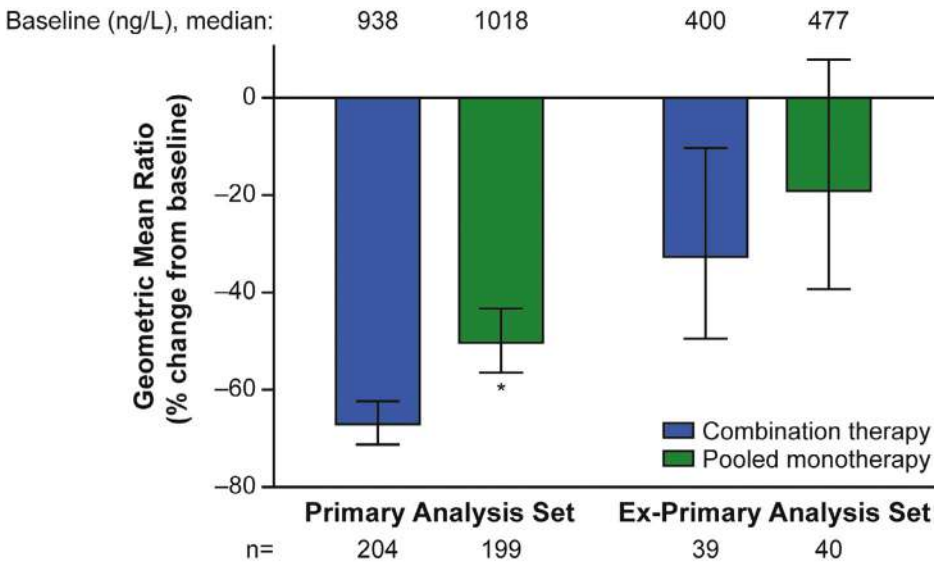

Figure 2 Percentage change in geometric mean NT-proBNP from baseline to Week 24 in primary analysis set and ex-primary analysis set patients. Vertical bars represent geometric mean ratios and vertical lines 95% confidence intervals. Statistical significance testing was not performed for ex-primary analysis set patients because of the relatively small sample size. Ex-primary analysis set is a post-hoc figure. *P<0.0001 versus combination therapy. NT-proBNP, N-terminal probrain natriuretic peptide.

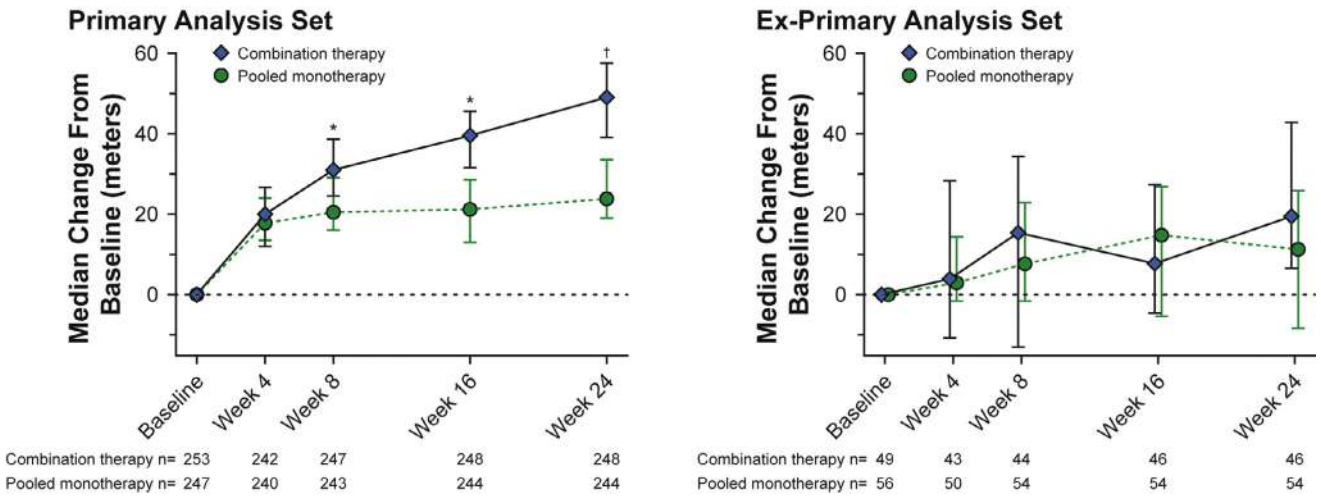

Figure 3 Median change in 6-minute walk distance from baseline through Week 24 in primary analysis set and ex-primary analysis set patients. Vertical lines represent 95% confidence intervals. Statistical significance testing was not performed for ex-primary analysis set patients because of the relatively small sample size. Ex-primary analysis set is a post-hoc figure. *$P<0.05$ between groups. †$P<0.0001$ between groups.

with either monotherapy in ex-primary analysis set patients but not in primary analysis set patients: diarrhea, cough, nasopharyngitis, pain in extremity, back pain, vomiting, myalgia, muscle spasms, and pyrexia.

Fewer primary analysis set than ex-primary analysis set patients (16% vs 31%) were permanently withdrawn from study drug because of AEs. This was observed in all treatment groups. Other reasons for study drug withdrawal occurred with similar frequency between primary analysis set and ex-primary analysis set patients. Rates of permanent study drug withdrawal because of AEs were 14% (primary analysis set patients) vs 33% (ex-primary analysis set patients) for patients on initial combination therapy, 19% vs 38% for those on ambrisentan monotherapy, and 15% vs 23% for those on tadalafil monotherapy. Rates of serious AEs (SAEs) were 36% (primary analysis set patients) vs 57% (ex-primary

Table 4 Summary of Common Adverse Events (>10% in Any Treatment Arm) with Higher Frequency on Combination Therapy versus Either Monotherapy Arm (>5% Difference) in Either Primary Analysis Set or Ex-Primary Analysis Set Patients

	Primary analysis set			Ex-primary analysis set		
Adverse event	Combination therapy ($n = 253$)	Ambrisentan monotherapy ($n = 126$)	Tadalafil monotherapy ($n = 121$)	Combination therapy ($n = 49$)	Ambrisentan monotherapy ($n = 26$)	Tadalafil monotherapy ($n = 30$)
Peripheral edema	115 (45)	41 (33)	34 (28)	20 (41)	17 (65)	9 (30)
Headache	107 (42)	41 (33)	42 (35)	18 (37)	10 (38)	11 (37)
Nasal congestion	54 (21)	19 (15)	15 (12)	4 (8)	6 (23)	2 (7)
Diarrhea	50 (20)	29 (23)	23 (19)	13 (27)	4 (15)	4 (13)
Dizziness	50 (20)	24 (19)	14 (12)	6 (12)	6 (23)	8 (27)
Cough	40 (16)	14 (11)	21 (17)	13 (27)	6 (23)	3 (10)
Flushing	38 (15)	18 (14)	11 (9)	3 (6)	0	3 (10)
Anemia	37 (15)	8 (6)	14 (12)	7 (14)	3 (12)	3 (10)
Nasopharyngitis	37 (15)	26 (21)	18 (15)	14 (29)	5 (19)	5 (17)
Pain in extremity	37 (15)	14 (11)	18 (15)	10 (20)	2 (8)	3 (10)
Back pain	31 (12)	13 (10)	18 (15)	12 (24)	3 (12)	4 (13)
Dyspepsia	29 (11)	5 (4)	14 (12)	3 (6)	0	4 (13)
Vomiting	28 (11)	11 (9)	12 (10)	7 (14)	2 (8)	1 (3)
Bronchitis	27 (11)	5 (4)	10 (8)	4 (8)	1 (4)	3 (10)
Myalgia	23 (9)	12 (10)	15 (12)	7 (14)	1 (4)	3 (10)
Muscle spasms	17 (7)	6 (5)	9 (7)	6 (12)	2 (8)	1 (3)
Pyrexia	11 (4)	7 (6)	3 (2)	6 (12)	0	1 (3)

Values are shown as *n* (%) of patients. Cut-off percentages were applied after rounding. Data are shown for both the primary analysis set and ex-primary analysis set even if the adverse event qualified to be listed for only one of the populations.

analysis set patients) for patients on initial combination therapy, 36% vs 58% for those on ambrisentan monotherapy, and 41% vs 43% for those on tadalafil monotherapy.

Discussion

At the time the AMBITION trial was conducted, ex-primary analysis set patients met the accepted hemodynamic definition of PAH (i.e., mean pulmonary arterial pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance >3 Wood units[10,11]), but by definition, they were older and had multiple risk factors for left ventricular diastolic dysfunction or minimally elevated pulmonary vascular resistance. Thus, it is not clear whether these patients should comprise a phenotypically distinct form of patients with WHO Group 1 PAH or whether they might be better characterized in an alternate group of pulmonary hypertension (e.g., WHO Group 2 patients who have been volume optimized). It is possible that our patients had true PAH; they may simply have been diagnosed early in the disease course or had multiple common comorbidities and just failed to meet the arbitrary criteria chosen for the study. In any event, these patients diverged from the more traditional PAH population studied in prior clinical trials.[15] This appears to reflect the changing demographics of patients with PAH reported in more recent PAH registries (i.e., older age, lower baseline 6MWD, and more risk factors for left ventricular diastolic dysfunction) and thus represents a substantial proportion of patients seen in clinical practice today.[1−7]

This analysis addresses the important question of whether or not ex-primary analysis set patients in the AMBITION trial experienced a benefit from initial combination treatment as compared with monotherapy. The treatment effects of initial combination therapy vs pooled monotherapy on the primary and some secondary efficacy end points were directionally the same for these patients as those for primary analysis set patients (Figure 4), albeit of a lower magnitude and not of statistical significance. The reduction in clinical failure events was driven primarily by fewer hospitalizations for worsening PAH in the combination arm, which was consistent in both populations.

In patients with PAH, the presence of multiple cardiovascular risk factors for left ventricular diastolic dysfunction may be associated with a blunted response to PAH-targeted therapy (e.g., change in symptom severity and change in 6MWD)[5] and may also be associated with more AEs. Indeed, our results showed a less pronounced response to treatment in ex-primary analysis set vs primary analysis set patients, as well as a greater incidence of SAEs (53% vs 37% across all treatment groups) and permanent study drug discontinuation because of AEs (31% vs 16%). These findings are in concordance with recent registry data and suggest that the optimal treatment approach for these patients should be determined on a case-by-case basis.

Our analysis of ex-primary analysis set patients represents, to our knowledge, the first analysis of such patients obtained in the context of a randomized controlled trial. Although these patients may respond less favorably to PAH-targeted therapies and have more adverse effects, these data are highly relevant to clinicians as they more frequently encounter this challenging patient population.

A limitation of our analysis was the relatively small sample size of ex-primary analysis set patients, which prohibited meaningful statistical testing in these patients. This population is, however, seen in clinical practice and represents an important population to further evaluate. One could argue that future clinical trials in PAH should employ the more stringent post-amendment entry criteria used in the AMBITION trial to avoid enrolling patients with characteristics that are similar to those of our ex-primary analysis set patients. The rationale for this viewpoint is that an attenuated response to treatment and less favorable tolerability in this population could prevent safe and effective PAH therapies from receiving regulatory approval. However, patients with this phenotype are frequently seen in the PAH clinic and large sample sizes are needed for assessment of morbidity/mortality end points, and these patients in the AMBITION trial did still appear to benefit from combination treatment as compared with monotherapy. From this perspective, it would seem reasonable for future clinical trials in PAH to employ the less rigorous pre-amendment entry criteria used in the AMBITION trial. This would allow enrollment within the same study of patients with characteristics that are similar to both of our patient groups. Stratification could be done to limit the number of patients with PAH enrolled with cardiovascular risk factors, thus minimizing any dilution of the treatment effect while providing the opportunity to analyze and describe this patient population more fully. Future clinical trials might also systematically collect additional baseline data (e.g., echocardiographic data and presence of atrial fibrillation) to better understand the characteristics of these patients.

This pre-specified analysis of the AMBITION trial compared patients with PAH who had (ex-primary analysis set) and did not have (primary analysis set) multiple risk factors for left ventricular diastolic dysfunction. Results showed that the efficacy of treatment with initial combination therapy vs pooled monotherapy was directionally similar for ex-primary analysis set patients as that for primary analysis set patients. However, in ex-primary analysis set patients, the response was attenuated for combination therapy over monotherapy and, for both treatment groups, clinical failure event rates were increased compared with primary analysis set patients. In addition, there were more SAEs and study drug withdrawals because of AEs in ex-primary analysis set patients than primary analysis set patients, possibly because of the high prevalence of risk factors for left ventricular diastolic dysfunction in the former group.

Data availability statement

GlaxoSmithKline makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com.

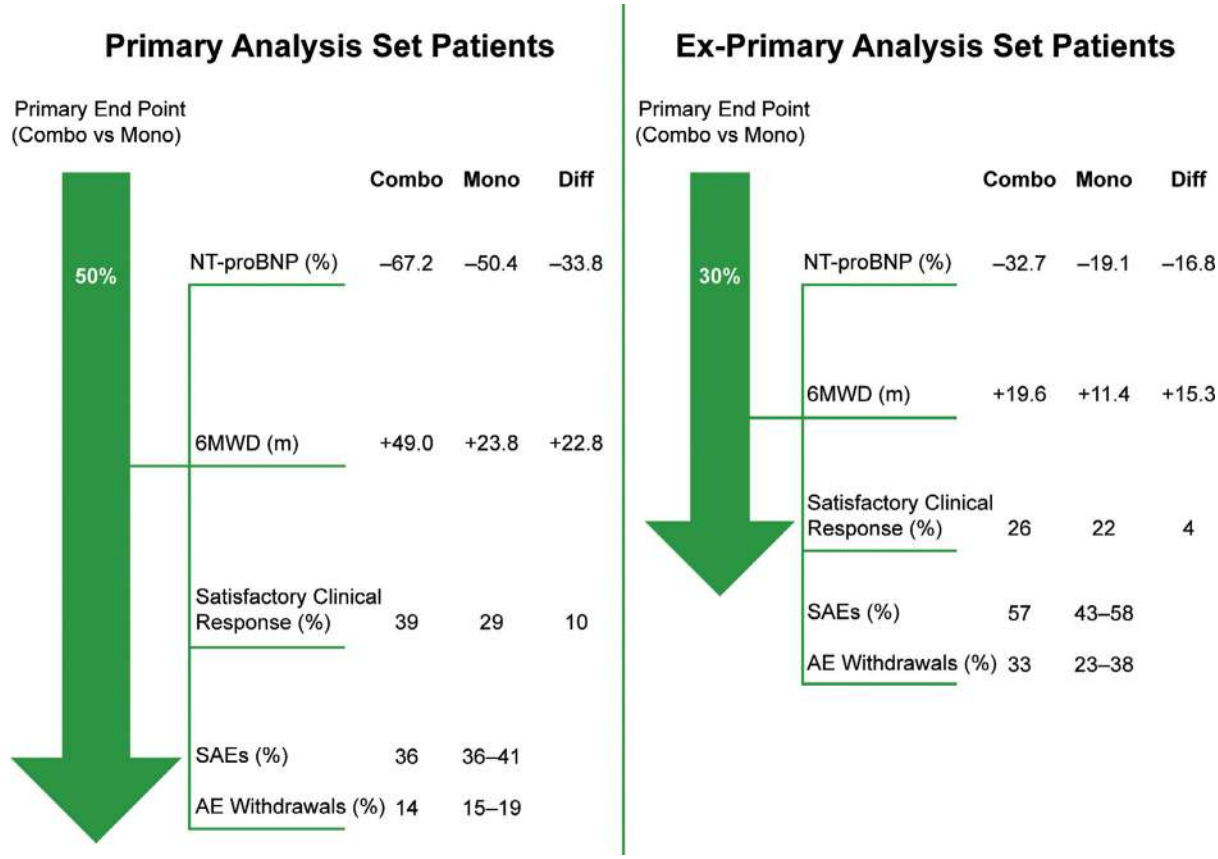

Figure 4 The effect of initial combination therapy compared with pooled monotherapy in primary analysis set and ex-primary analysis set patients from the AMBITION trial. Ex-primary analysis set patients had less favorable baseline characteristics (e.g., older age, lower 6MWD, and more comorbidities) and an attenuated treatment response compared with primary analysis set patients, but both populations had more favorable outcomes with initial combination therapy versus pooled monotherapy. Ex-primary analysis set patients had a higher incidence of SAEs and permanent study drug withdrawals because of adverse events. The primary end point was the time from randomization to first adjudicated clinical failure event; reduction in risk is presented. Other efficacy results are shown at Week 24 (change from baseline in geometric mean for NT-proBNP, median change from baseline for 6MWD). 6MWD, 6-minute walk distance; AE, adverse event; Combo, combination therapy with ambrisentan + tadalafil; Diff, treatment difference; Mono, pooled monotherapy with ambrisentan or tadalafil; NT-proBNP, N-terminal probrain natriuretic peptide; SAE, serious adverse event.

To access data for other types of GlaxoSmithKline-sponsored research, for study documents without patient-level data, and for clinical studies not listed, please submit an inquiry via the website. ClinicalTrials.gov identifier: NCT01178073.

Disclosure statement

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