ORIGINAL ARTICLE

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

ABSTRACT

BACKGROUND

Data on the effect of initial combination therapy with ambrisentan and tadalafil on long-term outcomes in patients with pulmonary arterial hypertension are scarce.

METHODS

In this event-driven, double-blind study, we randomly assigned, in a 2:1:1 ratio, participants with World Health Organization functional class II or III symptoms of pulmonary arterial hypertension who had not previously received treatment to receive initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group), 10 mg of ambrisentan plus placebo (ambrisentan-monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil-monotherapy group), all administered once daily. The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.

RESULTS

The primary analysis included 500 participants; 253 were assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group. A primary end-point event occurred in 18%, 34%, and 28% of the participants in these groups, respectively, and in 31% of the pooled-monotherapy group (the two monotherapy groups combined). The hazard ratio for the primary end point in the combination-therapy group versus the pooled-monotherapy group was 0.50 (95% confidence interval [CI], 0.35 to 0.72; P<0.001). At week 24, the combination-therapy group had greater reductions from baseline in N-terminal pro–brain natriuretic peptide levels than did the pooled-monotherapy group (mean change, −67.2% vs. −50.4%; P<0.001), as well as a higher percentage of patients with a satisfactory clinical response (39% vs. 29%; odds ratio, 1.56 [95% CI, 1.05 to 2.32]; P=0.03) and a greater improvement in the 6-minute walk distance (median change from baseline, 48.98 m vs. 23.80 m; P<0.001). The adverse events that occurred more frequently in the combination-therapy group than in either monotherapy group included peripheral edema, headache, nasal congestion, and anemia.

CONCLUSIONS

Among participants with pulmonary arterial hypertension who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy. (Funded by Gilead Sciences and GlaxoSmithKline; AMBITION ClinicalTrials.gov number, NCT01178073.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Galiè at the Department of Experimental, Diagnostic, and Specialty Medicine, University of Bologna, via Massarenti 9, Bologna 40138, Italy, or at nazzareno.galie@unibo.it.

*A complete list of investigators in the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study is provided in the Supplementary Appendix, available at NEJM.org.

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Regardless of the initiating trigger, pulmonary arterial hypertension results in the altered synthesis of a variety of vasoactive substances derived from the endothelium.[1] Current therapies for pulmonary arterial hypertension[2] target abnormalities in one of three intracellular pathways with signaling dysfunction: the prostacyclin, nitric oxide, or endothelin pathway.[1] However, no single class of drug is consistently effective in treating all patients, which suggests that no single pathway plays a dominant pathogenic role.[3,4]

Combination therapy with agents that target several different pathways may potentially increase the overall therapeutic effect on the mechanisms of this disease[5] and provide additional clinical benefits.[6-14] Most previous clinical studies that have investigated combination therapy for pulmonary arterial hypertension have evaluated sequential add-on therapies.[6-14] The effects of initial combination therapy on long-term clinical outcomes in patients who have not previously received treatment are unknown.[10,15,16]

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial investigated the efficacy and safety of initial combination therapy with oral, once-daily ambrisentan and tadalafil, as compared with monotherapy with either of these agents, in participants with previously untreated pulmonary arterial hypertension. We chose this combination because ambrisentan,[17] a selective endothelin-A–receptor antagonist, and tadalafil,[18] a phosphodiesterase type 5 inhibitor, target different intracellular pathways and do not have pharmacokinetic interactions.[19]

Methods

Study Design and Oversight

The AMBITION trial was a multicenter, randomized, double-blind, phase 3–4 study. The study was conducted between October 18, 2010 (first visit), and July 31, 2014 (last study visit), at 120 centers in 14 countries (the full list of centers and investigators is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol was designed by the authors and the sponsors (Gilead Sciences in the United States and GlaxoSmithKline in Canada, Europe, Japan, and Australia). The institutional review board at each center approved the study protocol. The monitoring and collection of the data were performed or overseen by the sponsors. The data were collected in electronic case-report forms, which were retained by the sponsors, with copies sent to the principal investigator at each site. A clinical endpoint committee, whose members were unaware of the study-group assignments and of the identity of the investigator, adjudicated all reported clinical events. Statistical analysis, which was performed by personnel at Hartington Statistics and Data Management, was funded and overseen by the sponsors.

All the authors had access to the data; contributed to the interpretation of the data, the writing of the manuscript, and the review of the final version; and were involved in the decision to submit the manuscript for publication. The first and last authors prepared the initial draft of the manuscript. Professional writing assistance for all drafts was provided by C4 MedSolutions and was paid for by the sponsors. The study drugs were provided by Gilead Sciences (ambrisentan), GlaxoSmithKline (ambrisentan), and Eli Lilly (tadalafil). All the authors assume full responsibility for the accuracy and completeness of the data and analyses and for fidelity of the manuscript to the study protocol, which is available at NEJM.org.

Selection of Participants

Participants were 18 to 75 years of age, weighed at least 40 kg, had World Health Organization (WHO) functional class II or III symptoms of pulmonary arterial hypertension, and had received a diagnosis of idiopathic pulmonary arterial hypertension, hereditary pulmonary arterial hypertension, or pulmonary arterial hypertension that was associated with connective tissue disease, drugs or toxins, human immunodeficiency virus (stable disease status), or repaired congenital heart defects (group 1 of the WHO classification of pulmonary hypertension). The diagnosis of pulmonary arterial hypertension was established by a ruling out of other known causes, according to the criteria in current guidelines.[2,20] For each participant, the mean pulmonary artery pressure was required to be 25 mm Hg or greater. Enrolled participants had either not received previous treatment with an approved therapy for pulmonary arterial hypertension or had received treatment for less than 14 days and had not received any approved therapy for pulmonary arterial hypertension within 7 days before

enrollment. A full set of inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix. All participants provided written informed consent.

A blinded review, performed by the steering committee and the sponsors, of demographic data from participants enrolled during the first 6 months of the study showed a relatively high prevalence of risk factors for left ventricular diastolic dysfunction, such as coronary artery disease, diabetes, or hypertension. The decision was therefore made to amend the eligibility criteria to exclude participants with three or more risk factors for left ventricular diastolic dysfunction and to set more stringent hemodynamic requirements. A comparison of the relevant inclusion and exclusion criteria in the initial protocol and in the subsequent amendment is provided in Table S2 in the Supplementary Appendix.

STUDY PROCEDURES

Eligible participants were stratified according to the underlying cause of pulmonary arterial hypertension (idiopathic or hereditary vs. nonidiopathic) and WHO functional class (II vs. III). Participants were randomly assigned, in a 2:1:1 ratio within each of the stratification strata, to receive ambrisentan and tadalafil (combination-therapy group), ambrisentan plus placebo (ambrisentan-monotherapy group), or tadalafil plus placebo (tadalafil-monotherapy group). Randomization was performed centrally by the study sponsors with the use of an interactive voice-response system. Ambrisentan and tadalafil were administered at an increasing dose to a target of 10 mg and 40 mg, respectively (Fig. S1 in the Supplementary Appendix).

If a primary end-point event occurred and the participant survived and remained in the study, investigators had the option either to discontinue the assigned monotherapy and start combination therapy with ambrisentan and tadalafil or to discontinue the assigned combination therapy or monotherapy and start prostanoid therapy or any other locally available therapy. In all cases, blinding of the initial randomized study-group assignment was maintained.

Efficacy and safety assessments were performed at the time of screening and at the time of randomization; at weeks 4, 8, 16, and 24 and every 12 weeks thereafter; and at the visit for the final assessment and the visit at the end of the study (Fig. S1 in the Supplementary Appendix). Laboratory safety assessments were performed monthly. A follow-up safety assessment was performed by telephone 30 days after the administration of the last dose of study medication.

OUTCOME MEASURES

The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite end point of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response. Specific definitions of the components of the primary end point are provided in Table 1. Supportive analyses were performed for the primary efficacy end point with the exclusion of the unsatisfactory clinical-response component and for the first occurrence of each of the individual components of the primary end point.

Prespecified secondary efficacy end points were the change from baseline to week 24 in N-terminal pro–brain natriuretic peptide (NT-proBNP) level, 6-minute walk distance, WHO functional class, and Borg dyspnea index (which measures perceived breathlessness[21]). We also calculated the percentage of participants with a satisfactory clinical response at week 24, which was defined as an increase of 10% from baseline in the 6-minute walk distance, with a reduction in symptoms to, or maintenance of, WHO functional class I or II and no events of worsening clinical condition before or at the week 24 visit. Safety assessments included laboratory measurements and evaluation of adverse events.

STATISTICAL ANALYSIS

On the basis of the recommendations of the steering committee, we originally projected an annual rate of clinical failure events of 10% in the combination-therapy group and of 20% in each of the monotherapy groups, with this projection leading to an estimated hazard ratio for clinical failure of 0.47 (i.e., a 53% lower risk of clinical failure with combination therapy than with each form of monotherapy). As noted above, the protocol was amended after the start of the study to reduce the likelihood of potentially enrolling participants with pulmonary hypertension due to left ventricular diastolic dysfunction and, after a blinded review of the event rate, to increase the sample size to preserve power. The primary-

Table 1. Components and Definitions of the Primary End Point.

Component*	Definition
Death from any cause	Existence of death certificate
Hospitalization for worsening pulmonary arterial hypertension	Any hospitalization for worsening pulmonary arterial hypertension, lung or heart and lung transplantation, atrial septostomy, or initiation of parenteral prostanoid therapy
Disease progression	A decrease of more than 15% from baseline in the 6-minute walk distance combined with World Health Organization (WHO) functional class III or IV symptoms at two consecutive visits separated by at least 14 days
Unsatisfactory long-term clinical response	Any decrease from baseline in 6-minute walk distance at two consecutive clinic visits after baseline separated by at least 14 days, and WHO functional class III symptoms assessed at two clinic visits separated by at least 6 months; assessed only among participants who were in the study for at least 6 months

* A clinical end-point committee, whose members were unaware of the study-group assignments and of the identity of the investigator, adjudicated all reported clinical events.

analysis set comprised all participants who underwent randomization, received a study drug, and met these amended entry criteria (Table S2 in the Supplementary Appendix); we also defined a modified intention-to-treat analysis set that comprised all participants who underwent randomization and received a study drug regardless of the amended entry criteria. We adopted an event-driven design; an adjudicated primary end-point event was required in 105 participants in the primary-analysis set to provide approximately 97% power to detect a 53% lower risk of clinical failure in the combination-therapy group than in the pooled-monotherapy group (the two monotherapy groups combined), at a type I error rate of 5%. Further information regarding the statistical analysis is provided in the Statistical Methods section in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The randomization, treatment, and follow-up of participants are shown in Figure S2 in the Supplementary Appendix. A total of 610 participants underwent randomization, 5 of whom did not receive a study medication. The modified intention-to-treat population included 605 participants; 302 were randomly assigned to the combination-therapy group, 152 to the ambrisentan-monotherapy group, and 151 to the tadalafil-monotherapy group. The primary-analysis set comprised 500 participants who fulfilled the amended entry criteria; 253 were randomly assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group.

Baseline characteristics were similar among the study groups in the primary-analysis set (Table 2). The mean age of the participants was 54.4 years, and 78% were women. Most participants had either idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension due to connective tissue disease, and 69% of participants had WHO functional class III symptoms. Baseline assessments of disease severity are shown in Table 3. The mean pulmonary artery pressure among participants was 48.7 mm Hg, and the mean 6-minute walk distance was 352.6 m.

FOLLOW-UP

In a post hoc analysis of data from the 500 participants in the primary-analysis set, the mean duration of use of a randomly assigned study medication from the start of therapy to the final-assessment visit was 517 days (550 days in the combination-therapy group and 484 days in the pooled-monotherapy group, P=0.03). In an additional post hoc analysis, the mean duration of study participation was 609 days (625 days in the combination-therapy group and 593 days in the pooled-monotherapy group, P=0.27).

A total of 64 participants (13%) withdrew from the study before having a primary end-point event. Of these participants, 8 subsequently had an event; that event was included in the analysis of

Table 2. Demographic and Baseline Characteristics.*

Characteristic	Combination-Therapy Group (N=253)	Pooled-Monotherapy Group (N=247)	Ambrisentan-Monotherapy Group (N=126)	Tadalafil-Monotherapy Group (N=121)
Age — yr	54.5±14.3	54.2±14.9	53.9±14.7	54.5±15.2
Female sex — no. (%)	188 (74)	200 (81)	100 (79)	100 (83)
Body-mass index†	27.7±6.3	28.1±6.8	27.6±6.5	28.6±7.2
Race — no. (%)‡				
White	233 (92)	213 (86)§	107 (85)	106 (88)
Nonwhite	20 (8)	34 (14)§	19 (15)	15 (12)
Region — no. (%)				
North America	116 (46)	112 (45)	51 (40)	61 (50)
Europe	129 (51)	128 (52)	72 (57)	56 (46)
Asia-Pacific: Japan and Australia	8 (3)	7 (3)	3 (2)	4 (3)
Coexisting conditions — no. (%)				
Hypertension	104 (41)	95 (38)	52 (41)	43 (36)
Diabetes	19 (8)	30 (12)	13 (10)	17 (14)§
Coronary artery disease	16 (6)	4 (2)§	2 (2)§	2 (2)§
Classification of pulmonary arterial hypertension — no. (%)				
Idiopathic	127 (50)	138 (56)	72 (57)	66 (55)
Heritable	7 (3)	7 (3)	3 (2)	4 (3)
Associated with connective-tissue disease	103 (41)	84 (34)	44 (35)	40 (33)
Associated with congenital heart disease	5 (2)	4 (2)	1 (1)	3 (2)
Associated with human immunodeficiency virus infection	5 (2)	4 (2)	2 (2)	2 (2)
Associated with drug use or toxin exposure	6 (2)	10 (4)	4 (3)	6 (5)
No history of therapy specifically for pulmonary arterial hypertension — no. (%)¶	242 (96)	235 (95)	120 (95)	115 (95)
Prior medications — no. (%)				
Oxygen	62 (25)	57 (23)	28 (22)	29 (24)
Anticoagulant	78 (31)	76 (31)	30 (24)	46 (38)
Calcium-channel blocker	70 (28)	69 (28)	32 (25)	37 (31)
Diuretic	142 (56)	139 (56)	72 (57)	67 (55)
Aldosterone antagonist	48 (19)	52 (21)	31 (25)	21 (17)
Median time from diagnosis to first administration of a study drug — days	20.0	25.0	20.5	29.0§

* Plus–minus values are means ±SD. The analyses were performed in the primary-analysis set, which comprised all participants who underwent randomization, received a study drug, and met amended entry criteria (which excluded participants with three or more risk factors for left ventricular diastolic dysfunction and set more stringent hemodynamic requirements than those in the original eligibility criteria). All baseline significance testing was performed post hoc. There were no significant differences among the groups except as noted.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race was self-reported.

§ P<0.05 vs. the combination-therapy group.

¶ A total of 19 participants (9 in the combination-therapy group and 10 in the pooled-monotherapy group) had received previous therapy specifically for pulmonary arterial hypertension that had been discontinued at least 14 days before the time of randomization, as required by the protocol. Four participants had missing responses at the time of the initial database freeze that were updated to "No" before the final database freeze.

Table 3. Disease Severity at Baseline.*

Variable	Combination-Therapy Group (N=253)	Pooled-Monotherapy Group (N=247)	Ambrisentan-Monotherapy Group (N=126)	Tadalafil-Monotherapy Group (N=121)
Hemodynamic variables				
Arterial blood pressure — mm Hg	90.1±12.9	89.1±11.7	89.5±12.1	88.8±11.3
Right atrial pressure — mm Hg	7.7±4.5	7.9±4.7	7.4±4.6	8.4±4.8
Pulmonary artery pressure — mm Hg	48.1±12.4	49.3±12.6	50.4±12.5	48.1±12.6
Pulmonary-capillary wedge pressure — mm Hg	8.4±3.1	8.9±3.4	8.6±3.3	9.3±3.5†
Cardiac index — liter/min/m^2	2.41±0.64	2.43±0.71	2.41±0.66	2.45±0.77
Pulmonary vascular resistance — dyne/sec/cm^5	824.1±467.0	825.7±402.1	852.4±394.7	798.0±409.4
NT-proBNP — ng/liter‡				
Median	938.0	1018.0	1171.0	869.0
Interquartile range	328.0–2484.5	334.0–1889.0	383.5–2091.0	297.0–1731.0
6-Minute walk distance — m				
Mean	353.5±87.9	351.7±91.8	354.2±92.3	349.2±91.6
Median	357.0	365.5	368.5	363.3
Interquartile range	292.0–425.3	297.5–425.2	310.0–427.5	287.0–421.5
WHO functional class — no. (%)				
II	76 (30)	79 (32)	38 (30)	41 (34)
III	177 (70)	168 (68)	88 (70)	80 (66)

* Plus–minus values are means ±SD. The analyses were performed in the primary-analysis set and include post hoc baseline significance testing.
† P=0.02 for the comparison with the combination-therapy group.
‡ A number of N-terminal pro–B-type natriuretic peptide (NT-proBNP) samples were lost or could not be analyzed. Analysis of NT-proBNP was performed on data from 236 participants in the combination-therapy group and 235 in the pooled-monotherapy group (120 in the ambrisentan-monotherapy group and 115 in the tadalafil-monotherapy group).

the primary end point. Survival status was available for all but 14 participants (3%) who withdrew from the study before the final-assessment visit, without having had an event; in the analysis of the primary end point, data from these participants were censored at the time of withdrawal.

PRIMARY EFFICACY END POINT

A total of 123 participants had a primary end-point event up to the time of the final-assessment visit (Table 4), including 46 (18%) in the combination-therapy group and 77 (31%) in the pooled-monotherapy group (43 [34%] in the ambrisentan-monotherapy group and 34 [28%] in the tadalafil-monotherapy group). Hospitalization for worsening pulmonary arterial hypertension was the primary end-point component with the largest observed difference in occurrence between the combination-therapy group and the pooled-monotherapy group (4% vs. 12%) (Table 4). In post hoc analyses, rates of hospitalization for any cause (calculated with the use of information from the serious-adverse-event and adjudication datasets) did not differ significantly among the groups (Table S3 in the Supplementary Appendix).

The hazard ratios for the primary end point were 0.50 (95% confidence interval [CI], 0.35 to 0.72) for the combination-therapy group versus the pooled-monotherapy group (P<0.001 by the stratified log-rank test) (Fig. 1A), 0.48 (95% CI, 0.31 to 0.72) for combination-therapy group versus the ambrisentan-monotherapy group (P<0.001) (Fig. 1B), and 0.53 (95% CI, 0.34 to 0.83) for the combination-therapy group versus the tadalafil-monotherapy group (P=0.005) (Fig. 1C). A forest plot of the adjudicated primary end point (clinical failure) and its components is shown in Figure S3 in the Supplementary Appendix.

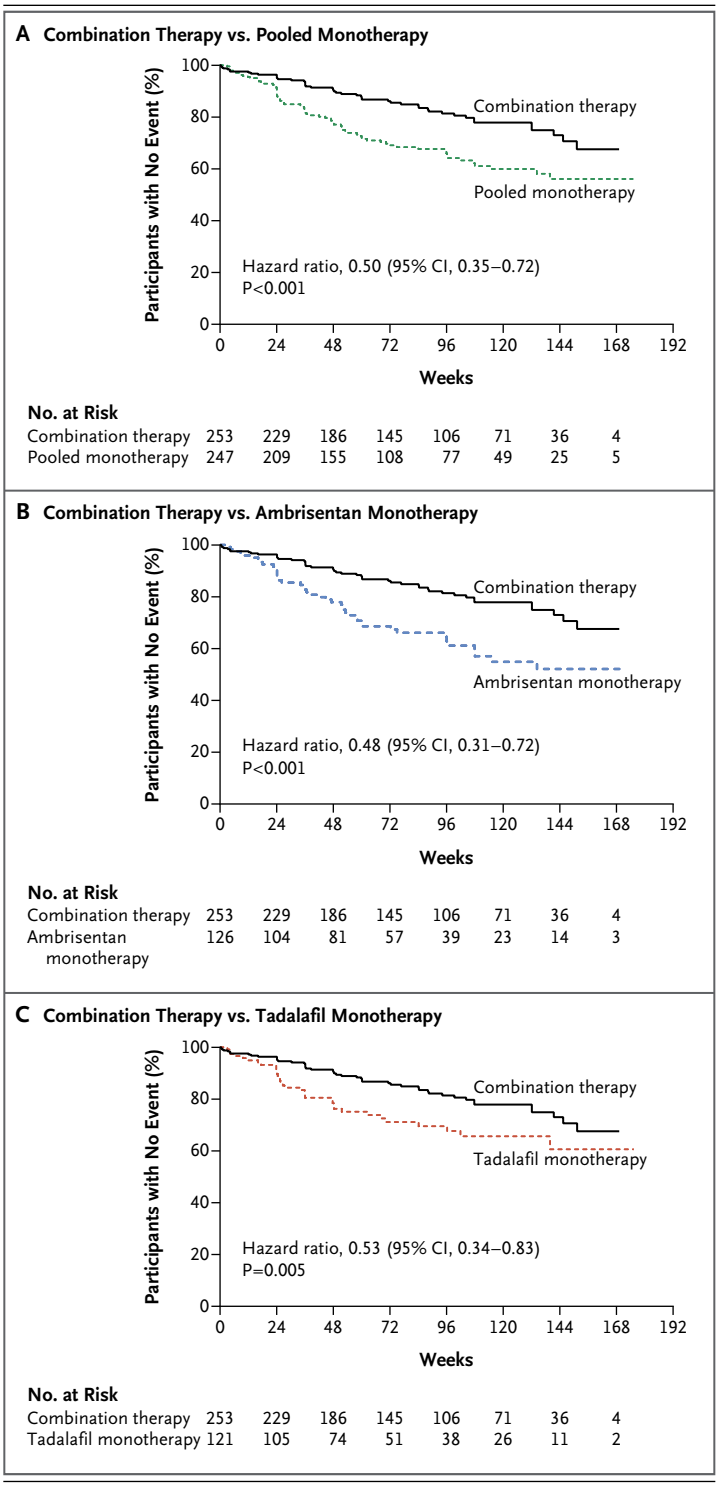
Table 4. Primary and Secondary Efficacy End Points.*

End Point	Combination-Therapy Group (N=253)	Pooled-Monotherapy Group (N=247)	Ambrisentan-Monotherapy Group (N=126)	Tadalafil-Monotherapy Group (N=121)
Primary end point				
First event of clinical failure — no. of participants (%)	46 (18)	77 (31)	43 (34)	34 (28)
Death	9 (4)	8 (3)	2 (2)	6 (5)
Hospitalization for worsening pulmonary arterial hypertension	10 (4)	30 (12)	18 (14)	12 (10)
Disease progression	10 (4)	16 (6)	12 (10)	4 (3)
Unsatisfactory long-term clinical response	17 (7)	23 (9)	11 (9)	12 (10)
Hazard ratio, combination therapy vs. monotherapy (95% CI)	Reference	0.50 (0.35 to 0.72)	0.48 (0.31 to 0.72)	0.53 (0.34 to 0.83)
P value	—	<0.001	<0.001	0.005
Secondary end points				
NT-proBNP level†				
Percentage change in geometric mean from baseline to week 24	−67.2	−50.4	−56.2	−43.8
P value	Reference	<0.001	0.01	<0.001
Satisfactory clinical response at week 24 — no. of participants/total no. (%)‡				
Yes	91/234 (39)	66/226 (29)	35/113 (31)	31/113 (27)
No	143/234 (61)	160/226 (71)	78/113 (69)	82/113 (73)
Unknown	19/253 (8)	21/247 (9)	13/126 (10)	8/121 (7)
Odds ratio, combination therapy vs. monotherapy (95% CI)	Reference	1.56 (1.05 to 2.32)	1.42 (0.88 to 2.31)	1.72 (1.05 to 2.83)
P value	—	0.03	0.15	0.03
6-Minute walk distance — m§				
Median (IQR) change from baseline to week 24	48.98 (4.63 to 85.75)	23.80 (−12.25 to 64.53)	27.00 (−14.00 to 63.25)	22.70 (−8.25 to 66.00)
P value	Reference	<0.001	<0.001	0.003
Change in WHO functional class at week 24 — no. of participants/total no. (%)§				
Improved	94/252 (37)	81/244 (33)	42/124 (34)	39/120 (33)
No change	146/252 (58)	147/244 (60)	73/124 (59)	74/120 (62)
Deteriorated	12/252 (5)	16/244 (7)	9/124 (7)	7/120 (6)
P value	Reference	0.24	0.30	0.36

* The analyses were performed in the primary-analysis set.
† Data were based on observed cases, with no imputation. A number of NT-proBNP samples were lost or could not be analyzed. Analysis of NT-proBNP was performed on data from 204 participants in the combination-therapy group and 199 in the pooled-monotherapy group (99 in the ambrisentan-monotherapy group and 100 in the tadalafil-monotherapy group).
‡ Data were based on observed cases, with no imputation.
§ Data were based on last-observation-carried-forward imputation or worst-case imputation. For participants who died or had an adjudicated hospitalization (and were unable to perform the test) on or before the date of the week 24 visit, worst-case imputation was used for missing data after death or adjudicated hospitalization (for 6-minute walk distance, missing data were imputed as zero; for WHO functional class, missing data were imputed as WHO functional class IV). For participants with missing data on 6-minute walk distance or WHO functional class before death or adjudicated hospitalization (or if these events did not occur in the case of the participant), last-observation-carried-forward imputation was used for missing data. Baseline data were not carried forward. The analysis of the 6-minute walk distance was performed on data from 248 participants in the combination-therapy group and 244 in the pooled-monotherapy group (124 in the ambrisentan-monotherapy group and 120 in the tadalafil-monotherapy group).

Figure 1. Kaplan–Meier Curves for the Probability of a First Adjudicated Primary End-Point Event.

The primary end point in a time-to-event analysis was the first event of clinical failure, which was a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response. The analyses were performed in the primary-analysis set, which comprised all participants who underwent randomization, received a study drug, and met amended entry criteria (which excluded participants with three or more risk factors for left ventricular diastolic dysfunction and set more stringent hemodynamic requirements than those in the original eligibility criteria).



Results of multiple sensitivity analyses of the primary end point are shown in Tables S4 through S7 and Figure S4 in the Supplementary Appendix. The results of these analyses were consistent with those of the primary analysis. A forest plot of the primary end point in subgroups defined according to underlying cause, WHO functional class, age, baseline 6-minute walk distance, geographic areas, and sex did not show any significant interactions between subgroup and treatment (Fig. S5 in the Supplementary Appendix).

SECONDARY EFFICACY END POINTS

Changes from baseline to week 24 in the prespecified secondary end points are shown in Table 4, and Table S8 in the Supplementary Appendix. Significant differences were observed in favor of combination therapy over pooled monotherapy, ambrisentan monotherapy, and tadalafil monotherapy with respect to the change from baseline in NT-proBNP level, the percentage of participants with a satisfactory clinical response (with the exception of combination therapy vs. ambrisentan monotherapy), and the change from baseline in 6-minute walk distance. Overall, the percentage of participants in the study groups who had an improvement in WHO functional class from baseline (Table 4) ranged from 33 to 37%, and the percentage of those who had no change in WHO functional class from baseline ranged from 58 to 62%. No significant differences among the study groups were found. Consequently, according to the prespecified hierarchical testing procedure (see the Statistical Methods section in the Supplementary Appendix), no further statistical comparisons were performed.

SAFETY

The most frequent adverse events are summarized in Table S9 in the Supplementary Appendix. Peripheral edema, headache, nasal congestion,

and anemia were more common in the combination-therapy group than in either monotherapy group, dizziness was more common in the combination-therapy group than in the tadalafil-monotherapy group, and syncope was more common in the tadalafil-monotherapy group than in the other groups; the incidence of hypotension was similar in the three study groups. The rate of discontinuation of a study drug and the rate of serious adverse events were similar in the three study groups (Table S9 in the Supplementary Appendix). The most common adverse events resulting in discontinuation of a study drug were peripheral edema and dyspnea. The most common serious adverse events were worsening of pulmonary arterial hypertension and pneumonia.

DISCUSSION

In the AMBITION trial, the risk of the primary end point of the first event of clinical failure was 50% lower among participants who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either drug. Most previous studies of combination therapy for patients with pulmonary arterial hypertension compared the addition of a therapy (investigational or approved) with placebo in participants already receiving background treatment with approved drugs (sequential combination therapy).[6-9,11-14] The AMBITION trial supports the rationale for targeting multiple pathways in pulmonary arterial hypertension and showed that early combination therapy can be beneficial.

The older age of our trial participants as compared with those in previous studies[8,13] raises the possibility that some of the participants enrolled in this trial, despite having met the hemodynamic criteria for pulmonary arterial hypertension, may have had left ventricular diastolic dysfunction, which is a common condition in patients in developed countries starting in the sixth decade of life.[22] Therapies for patients with pulmonary arterial hypertension (group 1 of the WHO classification) should generally not be used in patients with pulmonary hypertension due to left ventricular dysfunction (group 2 of the WHO classification) and can even be harmful in such patients. To limit the potential inclusion of patients with left ventricular diastolic dysfunction, we implemented an amendment excluding participants with multiple risk factors for this disorder.

The treatment effect with respect to the primary end point was driven mainly by a lower rate of hospitalization for pulmonary arterial hypertension in the combination-therapy group. Hospitalization for worsening pulmonary arterial hypertension is costly and is associated with a poor prognosis.[23-25] Rates of hospitalization for any cause did not differ significantly among the study groups, although these data were not collected prospectively and are thus subject to some uncertainty.

A separation in the curves for the primary end point was observed in the primary-analysis population at week 24, when an unsatisfactory clinical response, the fourth component of clinical failure, could first be assessed. Although the curves showed a tendency to converge after 144 weeks, the number of participants at this time point was insufficient to allow a meaningful comparison. Alternatively, this convergence after 144 weeks may suggest a waning beneficial effect of initial combination therapy over a longer observation period.

The analysis of secondary end points provides insights into the improvements achieved in the first 24 weeks of therapy. The rate of satisfactory clinical response, defined as a reduction in symptoms to, or maintenance of, WHO functional class I or II with improved exercise capacity and an absence of clinical events, was significantly higher in the combination-therapy group than in the pooled-monotherapy group but was not significantly higher in the combination-therapy group than in ambrisentan-monotherapy group. The magnitude of improvement in the 6-minute walk distance and of the decrease in NT-proBNP levels from baseline to week 24 that was observed in the combination-therapy group is similar to or greater than that observed in other studies,[6-8,11-14,26] in which the placebo-corrected treatment effects were amplified because there was either no change or a worsening in the condition of the participants receiving placebo.

This study has several limitations. Despite improvements in a variety of factors with combination therapy, we found no significant difference in WHO functional class among the study groups at week 24. Second, it is not known whether the findings in this study can be extrapolated to the use of other drugs in the same

classes or whether initial combination therapy with drugs representing other classes of approved therapies for pulmonary arterial hypertension would produce similar results. Third, our trial did not allow us to evaluate the possibility that response rates for participants in either of the monotherapy groups could have been increased if participants receiving one of the agents had been switched to the other agent. If some patients who do not have a response to one drug class have a response to the other drug class, as has been hypothesized, then switching classes as a treatment strategy might be as effective as combination therapy with potentially fewer side effects. Addressing this question would require a trial with a different design. Finally, it is unclear how the protocol amendment to exclude patients with risk factors for left ventricular diastolic dysfunction may affect the generalizability of these results, although the results of the sensitivity analysis that included all participants who received a study drug are encouraging in this regard.

In conclusion, in the AMBITION study, we found that among participants with pulmonary arterial hypertension who had not received previous treatment, the risk of the composite outcome of clinical failure was significantly lower among those who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either ambrisentan or tadalafil.

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APPENDIX

The authors' full names and academic degrees are as follows: Nazzareno Galiè, M.D., Joan A. Barberà, M.D., Adaani E. Frost, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Vallerie V. McLaughlin, M.D., Andrew J. Peacock, M.D., Gérald Simonneau, M.D., Jean-Luc Vachiery, M.D., Ekkehard Grünig, M.D., Ronald J. Oudiz, M.D., Anton Vonk-Noordegraaf, M.D., R. James White, M.D., Ph.D., Christiana Blair, M.S., Hunter Gillies, M.D., Karen L. Miller, Ph.D., Julia H.N. Harris, M.A., Jonathan Langley, B.Sc., and Lewis J. Rubin, M.D., for the AMBITION Investigators

The authors' affiliations are as follows: the Department of Experimental, Diagnostic, and Specialty Medicine, University of Bologna, Bologna, Italy (N.G.); Hospital Clínic–Institut d'Investigacions Biomèdiques August Pi i Sunyer and University of Barcelona, Barcelona, and Biomedical Research Networking Center on Respiratory Diseases, Madrid (J.A.B.); Baylor College of Medicine, Houston (A.E.F.); Universities of Giessen and Marburg Lung Center, Giessen (H.-A.G.), Hanover Medical School and German Center of Lung Research, Hanover (M.M.H.), and Thoraxklinik at University Hospital Heidelberg, Heidelberg (E.G.) — all in Germany; University of Michigan Health System, Ann Arbor (V.V.M.); Regional Heart and Lung Centre, Glasgow (A.J.P.), and GlaxoSmithKline, Uxbridge (J.H.N.H., J.L.) — both in the United Kingdom; Université Paris-Sud, Faculté de Médecine, and Assistance Publique–Hôpitaux de Paris, Centre de Référence de l'Hypertension Pulmonaire Sévère, Département Hospitalo-Universitaire Thorax Innovation, Service de Pneumologie, Hôpital de Bicêtre, Le Kremlin Bicêtre, INSERM Unité Mixté de Recherche S 999, Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson — all in France (G.S.); Universitaires de Bruxelles–Hôpital Erasme, Brussels (J.-L.V.); Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance (R.J.O.), Gilead Sciences, Foster City (C.B., H.G., K.L.M.), and University of California at San Diego, La Jolla (L.J.R.) — all in California; VU University Medical Center, Amsterdam (A.V.-N.); and the University of Rochester, Rochester, NY (R.J.W.).

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