ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Initial combination therapy with ambrisentan + tadalafil on pulmonary arterial hypertension–related hospitalization in the AMBITION trial

Jean-Luc Vachiéry, MD,[a] Nazzareno Galiè, MD,[b] Joan Albert Barberá, MD,[c] Adaani E. Frost, MD,[d] Hossein-Ardeschir Ghofrani, MD,[e] Marius M. Hoeper, MD,[f] Vallerie V. McLaughlin, MD,[g] Andrew J. Peacock, MD,[h] Gérald Simonneau, MD,[i,j] Christiana Blair, MS,[k] Karen L. Miller, PhD,[k,1] Jonathan Langley, BSc,[l] and Lewis J. Rubin, MD[m], for the AMBITION Study Group

From the [a]Cliniques Universitaires de Bruxelles–Hôpital Erasme, Brussels, Belgium; [b]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [c]Hospital Clínic–Institut d'Investigacions Biomèdiques August Pi i Sunyer and University of Barcelona, Barcelona, Spain, Biomedical Research Networking Center on Respiratory Diseases, Madrid, Spain; [d]Houston Methodist Hospital Lung Center and Weill Cornell Medical College, Houston, Texas, USA; [e]Universities of Giessen and Marburg Lung Center, Giessen, Germany; [f]Hannover Medical School and German Center of Lung Research, Hannover, Germany; [g]University of Michigan Health System, Ann Arbor, Michigan, USA; [h]Regional Heart and Lung Centre, Glasgow, Scotland; [i]Université Paris-Sud, Faculté de Médecine, Le Kremlin Bicêtre, France AP-HP, Centre de Référence de l'Hypertension Pulmonaire Sévère, Département Hospitalo–Universitaire Thorax Innovation, Service de Pneumologie, Hôpital de Bicêtre, Le Kremlin Bicêtre, France; [j]UMR_S 999, INSERM, Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France; [k]Gilead Sciences, Inc., Foster City, California, USA; [l]GlaxoSmithKline, Uxbridge, UK; and the [m]University of California at San Diego, La Jolla, California, USA.

KEYWORDS:
ambrisentan;
hospitalization;
pulmonary arterial hypertension;
tadalafil;
combination therapy;
clinical trial

BACKGROUND: In the randomized, double-blind, event-driven AMBITION study, initial combination therapy with ambrisentan and tadalafil was associated with a 50% reduction in risk of clinical failure (first occurrence of all-cause death, hospitalization for worsening pulmonary arterial hypertension [PAH], disease progression, or unsatisfactory long-term clinical response) vs pooled monotherapy. These results were primarily driven by a reduction in PAH-related hospitalization in the combination therapy group, although a significant effect was not observed in a post-hoc analysis of all-cause hospitalization.

METHODS: The effect of initial combination therapy with ambrisentan and tadalafil in AMBITION was further explored to study PAH-related hospitalization, which was not reported in the primary publication.

RESULTS: Initial combination therapy was associated with a 63% reduction in risk of PAH-related hospitalization when compared with pooled monotherapy (hazard ratio [HR] 0.372, 95% confidence interval [CI] 0.217 to 0.639, $p = 0.0002$). For every 9 patients treated with combination therapy vs monotherapy, 1 PAH-related hospitalization could be prevented over a 1-year period. Serious adverse events leading to hospitalization, not necessarily PAH-related, occurred in 87 of 253 (34%) and 89 of 247 (36%) of patients on combination therapy and pooled monotherapy, respectively (post-hoc summary).

[1]No longer affiliated with Gilead, Inc.

Reprint requests: Jean-Luc Vachiéry, MD, Département de Cardiologie Cliniques Universitaires de Bruxelles–Hôpital Erasme, 808 Route de Lennik, 1070 Brussels, Belgium. Telephone: +3225555602. Fax: +3225556652.

E-mail address: jeanluc.vachiery@erasme.ulb.ac.be

https://doi.org/10.1016/j.healun.2018.11.006

CONCLUSIONS: Initial combination therapy with ambrisentan and tadalafil was found to reduce the risk of PAH-related hospitalization by 63% compared with pooled monotherapy.
J Heart Lung Transplant 2019;38:194−202

Pulmonary arterial hypertension (PAH) is a severe condition associated with high rates of mortality and hospitalization.[1−3] Management strategies for PAH have evolved, moving from monotherapy to sequential combination therapy in case of inadequate clinical response.[4,5] More recently, clinical experience showed favorable trends for initial combination therapy over monotherapy in uncontrolled or small controlled studies.[6−8] Such a strategy is supported by the potential benefit of targeting multiple pathways at the same time.[9,10]

Initial combination therapy, compared with initial monotherapy, was studied with ambrisentan, an endothelin type A receptor antagonist, and tadalafil, a phosphodiesterase-5 inhibitor, in the phase 3/4, randomized, double-blind, multicenter, active-controlled, event-driven AMBITION study (NCT01178073).[11] As reported in the primary publication,[11] initial combination therapy was associated with a 50% reduction in the risk of clinical failure (first occurrence of all-cause death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) vs monotherapy (hazard ratio [HR] 0.502, 95% confidence interval [CI] 0.348 to 0.724, $p = 0.0002$). These results were driven by a reduction in PAH-related hospitalization as a first event in the combination arm. A post-hoc analysis included in the primary publication showed no statistically significant difference between the treatment groups in rates of *first* all-cause hospitalization; this analysis included hospitalizations for worsening PAH and serious adverse events (SAEs) leading to hospitalizations (not necessarily related to PAH).[11]

Hospitalizations are recognized as important endpoints in chronic heart failure and PAH trials.[12−14] Therefore, the objective of this exploratory analysis of the AMBITION study was to further assess both the PAH-related hospitalization component of the pre-specified primary end-point and SAEs leading to hospitalization. Specifically, the effect of initial combination therapy with ambrisentan and tadalafil on PAH-related hospitalization was further explored, including post-hoc analysis within patient subgroups and post-hoc covariate analysis of factors potentially associated with an increased risk of PAH-related hospitalization. To expand on the data reported in the primary publication, we also present the incidence rates of *all* SAEs leading to hospitalization, irrespective of cause, as well as the most common investigator-reported causes (post-hoc summaries).

Methods

Study design

The design of the AMBITION study has been described previously.[11] Patients were stratified by PAH etiology (idiopathic or heritable vs non-idiopathic) and World Health Organization functional class (WHO FC II vs III) and randomized 2:1:1 to receive combination therapy with ambrisentan and tadalafil, monotherapy with ambrisentan, or monotherapy with tadalafil. Ambrisentan was up-titrated from 5 to 10 mg at Week 8, and tadalafil was up-titrated from 20 to 40 mg at Week 4. All doses were administered once daily. Efficacy and safety were assessed at screening; randomization; Weeks 4, 8, 16, and 24, then subsequently every 12 weeks; and at the final assessment and end-of-study visits. At the investigator's discretion, patients who had a clinical failure event and remained in the study could (in a blinded fashion) discontinue their assigned monotherapy and start combination therapy (ambrisentan and tadalafil) or they could discontinue their assigned treatment (monotherapy or combination therapy) and start prostanoid or any other locally available therapy.

Patients

Eligible patients were PAH treatment-naive adults (18 to 75 years old) with WHO FC II or III symptoms; a diagnosis of idiopathic, heritable, or non-idiopathic PAH; and mean pulmonary arterial pressure ≥25 mm Hg.[11] All patients provided written informed consent to participate in thw atusy.

Assessments

All reported clinical failure events were adjudicated by an independent clinical end-point committee that was blinded to treatment assignment and investigator. Hospitalization for worsening PAH (i.e., PAH-related hospitalization) was a component of the composite primary end-point of time from randomization to first clinical failure event. PAH-related hospitalization was defined as any hospitalization for worsening PAH, lung or heart/lung transplant, atrial septostomy, or initiation of parenteral prostanoid therapy. Worsening PAH was defined as worsening breathlessness, fluid retention, angina, or syncope supported by evidence from physical examination, routine blood tests, electrocardiogram, and chest radiography; deterioration in exercise performance requiring urgent investigation and treatment; or disease progression (>15% decrease from baseline in 6-minute walk distance combined with WHO FC III or IV symptoms at 2 consecutive post-baseline clinic visits separated by ≥14 days). Time to first hospitalization for worsening PAH was a prespecified supportive analysis of the primary end-point. Data for length of hospital stay were not collected.

Herein we report SAEs requiring hospitalization or prolongation of existing hospitalization, summarized by system organ class and preferred term. SAEs that occurred >30 days after the last dose of study drug and, for this analysis, those that occurred after a clinical failure event and while the patient was on blinded combination therapy, were not included. SAEs were reviewed by the chair of the clinical end-point committee and, if there was suspicion of a hospitalization being PAH-related, a dossier was prepared and adjudicated by the full clinical end-point committee.

As PAH-related hospitalizations constituting a primary end-point event were reported independently of SAE hospitalizations, there may be overlap in the numbers reported between the two. A PAH-related hospitalization, as a component of the composite primary end-point, was not necessarily an SAE hospitalization. Similarly, an SAE hospitalization was not necessarily a primary end-point event (e.g., due to adjudication); also, multiple SAEs may have contributed to a single hospitalization.

Statistical analyses

The primary efficacy comparison was between combination therapy and pooled monotherapy. Comparisons between combination therapy and individual monotherapies were performed only if the primary comparison was statistically significant. The analyses herein were performed on the primary analysis data set, which is the same as that used in the primary publication. Results for the modified intention-to-treat population are summarized in the Supplementary Material (available online at www.jhltonline.org/). The pre-specified time to first hospitalization for worsening PAH treatment difference was tested using the stratified log-rank test, adjusted for etiology of PAH (idiopathic/heritable PAH vs non-idiopathic PAH) and WHO FC (II vs III). A Cox proportional hazards regression model was used to calculate the HR and 95% CI. Treatment differences over time were analyzed using the Kaplan−Meier method. Post-hoc analyses were conducted by patient subgroups based on etiology of PAH (idiopathic/heritable vs non-idiopathic), baseline WHO FC (II vs III), median baseline 6-minute walk distance (<363.7 vs ≥363.7 m), geographic region (North America vs rest of world), sex, and median baseline age (<57 vs ≥57 years).

A post-hoc Cox proportional hazards covariate analysis of time to first hospitalization for worsening PAH considered the following variables for inclusion in the final model: treatment (combination vs pooled monotherapy); region (North America vs rest of world); sex; age; baseline 6-minute walk distance; baseline cardiac output; baseline right atrial pressure; baseline pulmonary vascular resistance; and log-transformed baseline N-terminal pro−brain natriuretic peptide (NT-proBNP)—all either below or above the median, using a backward elimination procedure. The stratification variables (PAH etiology and WHO FC, as just defined) were also included as covariates to investigate the significance of the (2-way) interactions effect between treatment and the 2 stratification variables, using a significance level of 10%. HRs and 95% CIs were calculated from the Cox proportional-hazards model. For censored patients, time was calculated as number of days from randomization to the final assessment visit.

Results

Patients

Of 500 patients in the primary analysis set, 253 received combination therapy with ambrisentan and tadalafil, and 247 received monotherapy with either drug. Of note, approximately twice as many patients were subsequently treated with combination therapy in the pooled monotherapy arm compared with the combination therapy arm (60 [24%] vs 28 [11%]). Baseline characteristics were similar between groups.[11]

Total exposure to therapy was 408 patient-years for those who received combination therapy and 382 patient-years for those who received monotherapy.

PAH-related hospitalization

Pre-specified analysis. As reported previously,[11] initial combination therapy was associated with a statistically significant 63% reduction in the risk of hospitalization for worsening PAH, compared with pooled monotherapy, from randomization to the final assessment visit (Figure 1). PAH-related hospitalizations from randomization through final assessment visit were reported in 19 (8%) patients in the combination therapy arm and 44 (18%) patients in the pooled monotherapy arm (HR 0.372, 95% CI 0.217 to 0.639, $p = 0.0002$). The comparisons with the ambrisentan monotherapy group (HR 0.323, 95% CI 0.179 to 0.583, log rank $p < 0.0001$) and the tadalafil monotherapy group (HR 0.442, 95% CI 0.229 to 0.853, log rank $p = 0.0124$) were also statistically significant. Pre-specified analysis of PAH-related hospitalization from randomization through end of study showed similar findings (Table 1).

The pre-specified Kaplan−Meier probabilities of a patient having a PAH hospitalization by 1 year were 2.1% for combination therapy and 14.3% for pooled monotherapy. Therefore, for every 9 patients (1/[0.143 to 0.021] = 8.2 patients, rounded up to 9) treated with combination therapy vs monotherapy, 1 PAH-related hospitalization could be prevented over the course of 1 year.

Post-hoc summary. Nineteen (8%) patients had a PAH-related hospitalization in the combination therapy group, and 5 (2%) had >1 PAH-related hospitalization (Table 2). Forty-four (18%) patients had a PAH-related hospitalization in the pooled monotherapy group, and 9 (4%) had >1 PAH-related hospitalization. Hospitalization for initiation of parenteral prostanoids and other hospitalization for worsening PAH were the most common reasons for PAH-related hospitalization. The rate of hospitalizations for worsening PAH per 100 patient-years was 4.7 with combination therapy and 11.5 in the pooled monotherapy group (Table 2). The corresponding rates of all-cause hospitalization, which were calculated post hoc using information from both the SAE and adjudicated event databases and included in the primary publication's supplementary appendix,[11] were numerically lower on combination therapy (30 events per 100 patient-years) compared with pooled monotherapy (37 events per 100 patient-years), although this was not significantly different.

Post-hoc analysis revealed that 5 of 253 (2%) patients in the combination group had hospitalizations for PAH worsening during the first year of treatment, compared with 31 of 247 (13%) in the pooled monotherapy group (Figure 2).

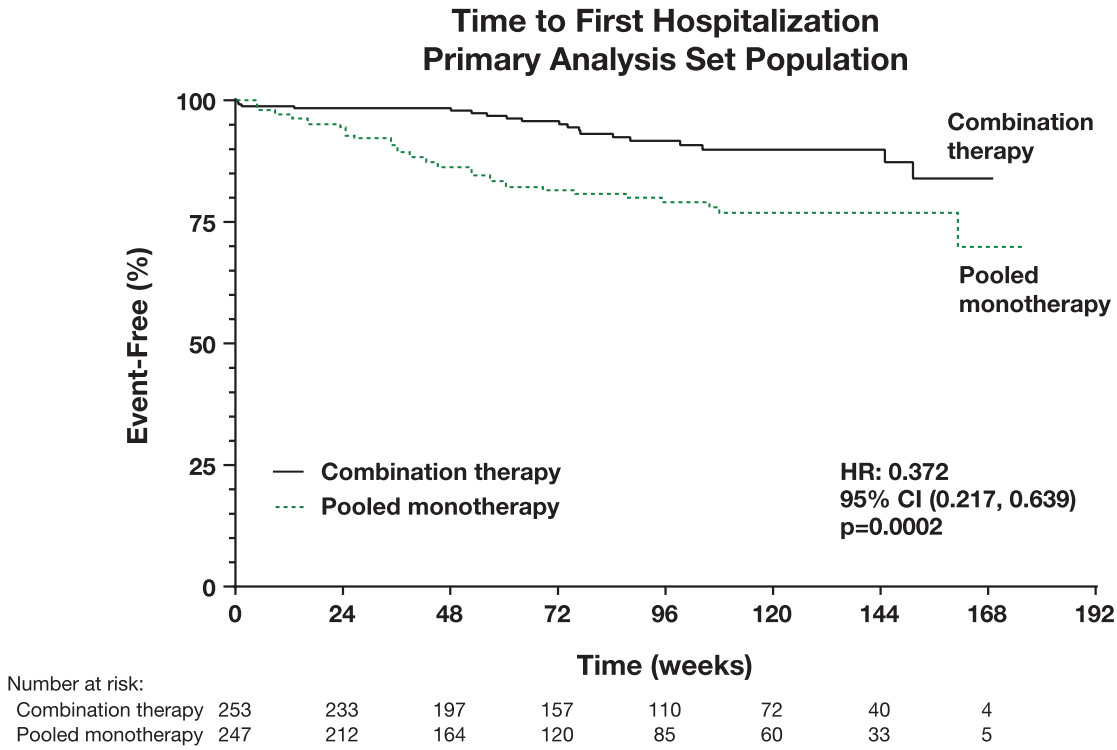

Figure 1 Kaplan–Meier plot of time to first hospitalization for worsening PAH with combination therapy vs pooled monotherapy (from randomization to the final assessment visit). CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension.

Post-hoc subgroup and covariate analyses

The risk of hospitalization for worsening PAH was lower with combination therapy vs pooled monotherapy in all subgroups analyzed (Figure 3). Among patients with WHO FC II symptoms at baseline, no PAH-related hospitalization occurred with combination therapy, whereas 11 (14%) patients in the pooled monotherapy group had a PAH-related hospitalization.

Factors associated with an increased risk of hospitalization for worsening PAH were: being in the pooled monotherapy group; a lower baseline 6-minute walk distance (< median = 363.7 meters); and higher baseline NT-proBNP level (log-transformed value ≥ median value of 6.912 ng/liter) (Table 3).

Post-hoc serious adverse events leading to hospitalization

The most common (≥3%) SAEs leading to hospitalization, regardless of cause, are summarized by treatment group in Table 4. The leading causes were pneumonia and worsening of PAH (each reported by 4% of patients) in the combination therapy arm, worsening of PAH (8%) and pneumonia (6%) in the ambrisentan monotherapy arm, and worsening of PAH (7%) and syncope (4%) in the tadalafil monotherapy arm.

Modified intention-to-treat population

Results for the modified intention-to-treat population were similar to those of the primary analysis set (see Tables S1 to S4 in the Supplementary Material online).

Discussion

This exploratory analysis of the AMBITION study has shown that initial combination therapy with ambrisentan and tadalafil reduced the risk of PAH-related hospitalization compared with monotherapy with either drug. From post-hoc analyses, the benefit of combination therapy in reducing the risk of PAH-related hospitalization vs pooled monotherapy was observed across all subgroups analyzed,

Table 1 Summary of First PAH-related Hospitalization from Randomization to End of Study

	Combination therapy ($N = 253$)	Pooled monotherapy ($N = 247$)
Number (%) of patients with first PAH-related hospitalization	20 (8%)	48 (19%)
KM probability of event at 1 year (% [95% CI])	2.07 (0.86 to 4.91)	14.54 (10.55 to 19.86)
Hazard ratio (95% CI)		0.363 (0.215 to 0.611)
p-value		<0.0001

CI, confidence interval; KM, Kaplan–Meier; PAH, pulmonary arterial hypertension.

Table 2 Summary of Hospitalizations for Worsening PAH by Type (from Randomization to Final Assessment Visit), and Hospitalization Rate Adjusted for Exposure

	Combination therapy ($N = 253$)	Pooled monotherapy ($N = 247$)
Patients with ≥1 hospitalization for worsening PAH	19 (8%)	44 (18%)
Reason for first hospitalization for worsening PAH		
Initiation of parenteral prostanoids	10	15
Atrial septostomy	0	1
Other hospitalization for worsening PAH	9	28
Post-hoc summaries		
Number (%) of patients with:		
0 hospitalization for worsening PAH	234 (92%)	203 (82%)
1 hospitalization for worsening PAH	14 (6%)	35 (14%)
>1 hospitalization for worsening PAH	5 (2%)	9 (4%)
Total exposure (patient-years)	408	382
Rate of hospitalization for worsening PAH per 100 patient-years	4.7	11.5

Data expressed as number (%) or as number. PAH, pulmonary arterial hypertension.

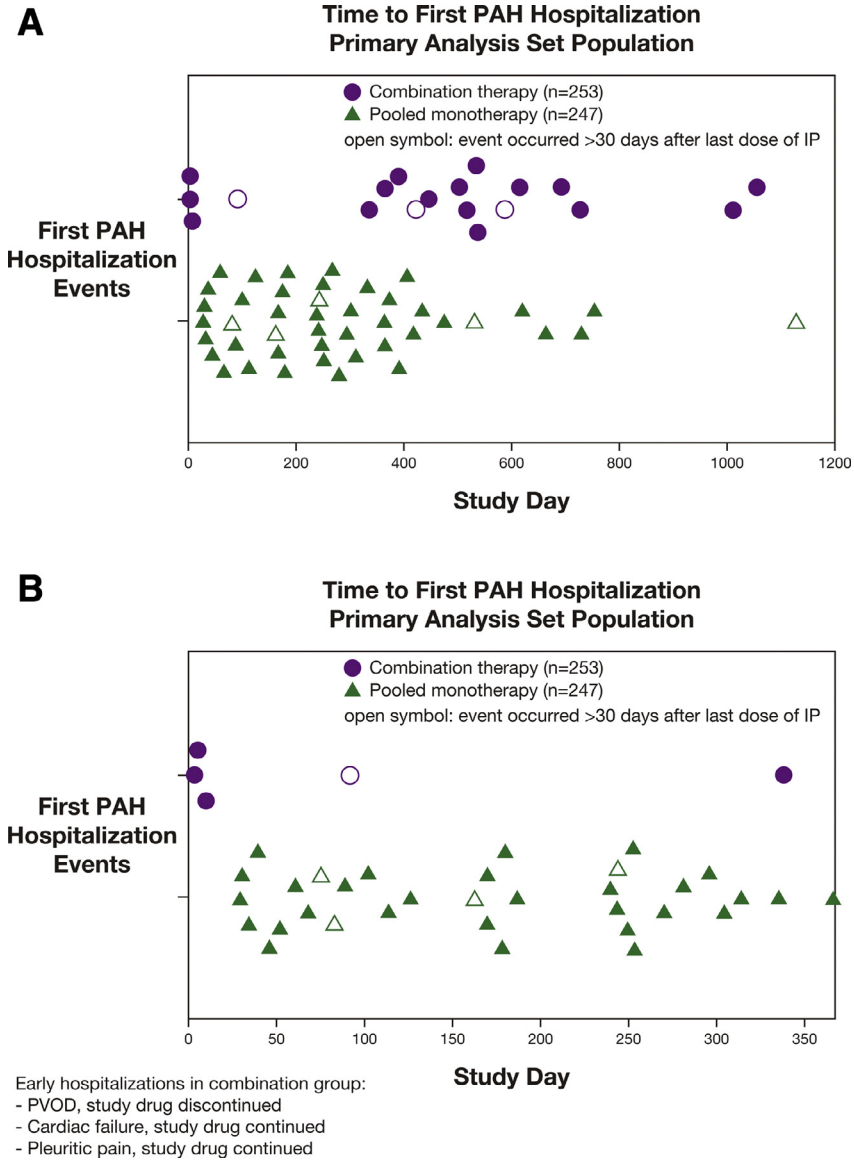

Figure 2 Scatterplot of time to occurrence of first PAH hospitalization during (A) the entire study period (A) and the first year (B). IP, investigational product; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease.

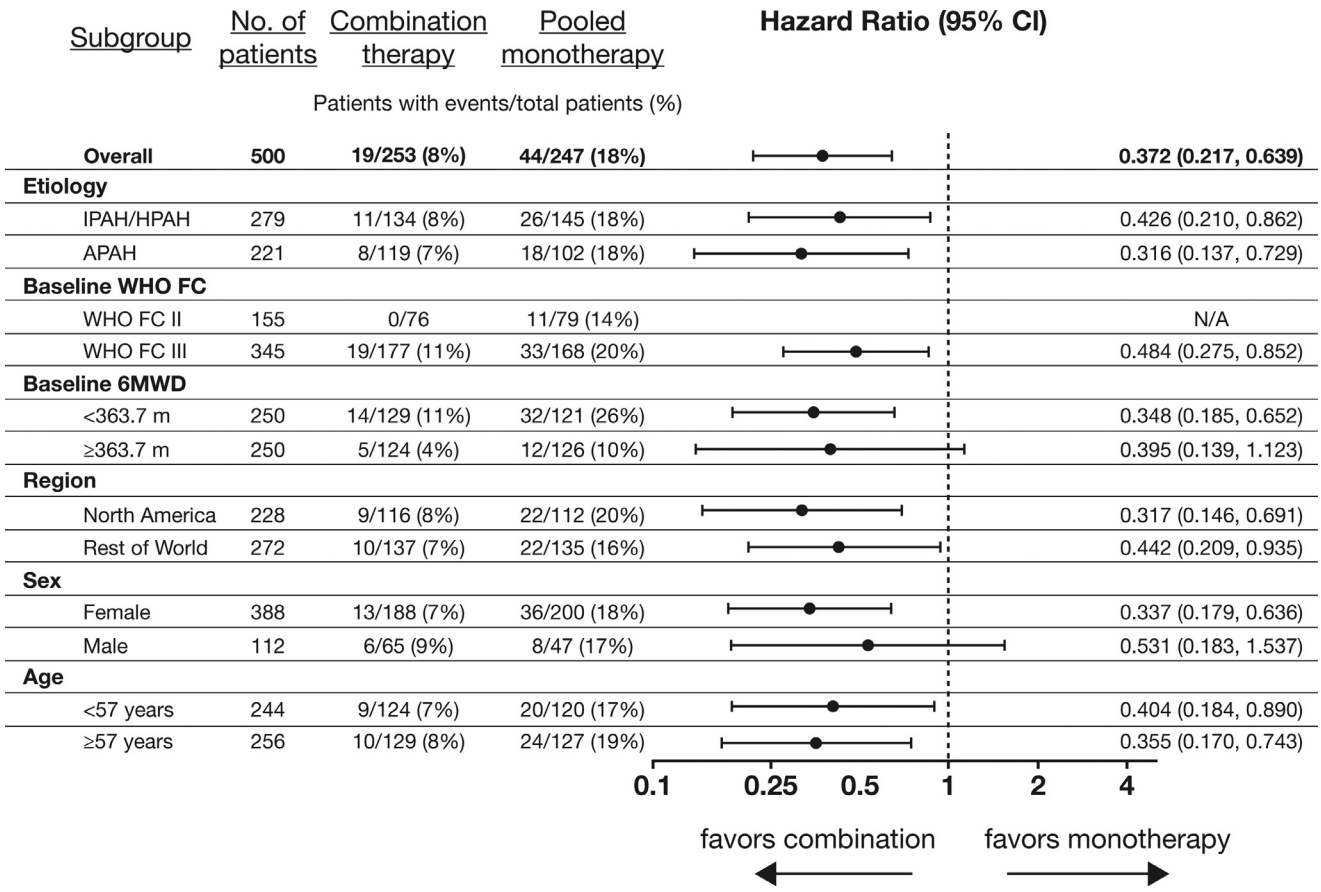

Figure 3 Forest plot of time to first hospitalization for worsening PAH with combination therapy vs pooled monotherapy by pre-defined subgroup (from randomization to the final assessment visit). 6MWD, 6-minute walk distance; APAH, associated pulmonary arterial hypertension; CI, confidence interval; FC, functional class; IPAH/HPAH, idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension; WHO, World Health Organization.

including those based on PAH etiology, baseline WHO FC, baseline 6-minute walk distance, geographic region, sex, and baseline age. Repeated PAH-related hospitalization was uncommon, possibly due to escalation of therapy after the first hospitalization. Factors identified in post-hoc analysis as conferring an increased risk of PAH-related hospitalization, in addition to pooled monotherapy, were lower baseline 6-minute walk distance and higher baseline NT-proBNP level, consistent with previous analyses showing similar associations between these parameters and survival.[15,16] A summary of SAEs leading to hospitalization showed lower rates in the initial combination therapy and ambrisentan monotherapy groups (34% and 33%, respectively) compared with the tadalafil monotherapy group (40%).

The current analysis adds to a limited number of event-driven, randomized, controlled trials providing data on hospitalization in patients with PAH. Our findings are consistent with those of the SERAPHIN and GRIPHON studies, which showed a benefit of sequential combination therapy.[3,17] In contrast, the COMPASS 2 study did not show a benefit of sequential combination therapy[18]; this may be explained, in part, by the study design, which included a long recruitment time and likely a low power to detect a difference between groups.[19]

Table 3 Post-hoc Covariate[a] Analysis of Time to First Hospitalization for Worsening PAH (from Randomization to Final Assessment Visit)

Variable included in final model	Hazard ratio	95% CI
Treatment (combination vs pooled monotherapy)	0.323	0.183 to 0.568
Baseline 6MWD ≥ vs < median (363.7 m)	0.385	0.209 to 0.711
Baseline NT-proBNP (log-transformed) ≥ vs < median (6.912 ng/liter)	3.216	1.701 to 6.079

6MWD, 6-minute walk distance; CI, confidence interval; NT-proBNP, N-terminal pro–brain natriuretic peptide; PAH, pulmonary arterial hypertension.
[a]Covariate dichotomized by median.

Table 4 Post-hoc Summary of Serious Adverse Events Leading to Hospitalization Regardless of Cause (≥3% on Any Randomized Treatment) (from Randomization to Final Assessment Visit)

SAE by system organ class preferred term	Combination therapy (n = 253)	Ambrisentan monotherapy (n = 126)	Tadalafil monotherapy (n = 121)
Patients with any SAE leading to hospitalization	87 (34%)	41 (33%)	48 (40%)
Respiratory, thoracic, or mediastinal disorders	34 (13%)	18 (14%)	17 (14%)
Pulmonary hypertension[a]	11 (4%)	10 (8%)	9 (7%)
Dyspnea	8 (3%)	2 (2%)	3 (2%)
Infections and infestations	28 (11%)	14 (11%)	16 (13%)
Pneumonia	11 (4%)	7 (6%)	4 (3%)
Cardiac disorders	13 (5%)	7 (6%)	9 (7%)
Cardiac failure	2 (<1%)	4 (3%)	1 (<1%)
Nervous system disorders	7 (3%)	8 (6%)	9 (7%)
Syncope	6 (2%)	3 (2%)	5 (4%)
Blood and lymphatic system disorders	7 (3%)	1 (<1%)	5 (4%)
Anemia	4 (2%)	1 (<1%)	4 (3%)

Data expressed as number (%). SAE, serious adverse event.

[a]In each case, the investigator reported the events using additional text not captured in the preferred term, describing this as worsening of pulmonary hypertension. However, an adverse event report of worsening pulmonary hypertension does not necessarily become a primary end-point event, which had specific criteria (see text for details).

Hospitalization for worsening PAH is common in clinical practice[20] and associated with poor survival. In the REVEAL registry, in-hospital mortality among newly diagnosed PAH patients was almost 4-fold greater than non–PAH-related hospitalizations[21] and 3-year post-discharge survival after first hospitalization was significantly lower for PAH-related vs non–PAH-related hospitalizations. The economic burden is substantial, with initial hospitalizations among commercially insured patients costing $46,070 and average re-admissions costing $73,066 when PAH was the principal diagnosis.[20] The observed incidence of PAH-related hospitalization, and its associated costs and mortality, together with the lack of correlation between changes in other parameters (e.g., 6-minute walk distance, cardiopulmonary hemodynamics) and clinical events,[22,23] underscores the importance of this end-point in clinical trial designs. The cost associated with hospitalization is lower, albeit still considerable, when the principal diagnosis is something other than PAH ($43,569 for initial hospitalizations, $41,438 for average re-admissions).[20]

The fact that rates of all-cause hospitalizations in the AMBITION study were approximately 2- to 4-fold greater than rates of PAH-related hospitalization is an important finding. In addition, there was no statistically significant difference between initial combination therapy and combined monotherapy in this post-hoc analysis. As AMBITION is the first study to assess the effects of initial oral combination therapy on outcome, there are no data available to put this observation into perspective. In the predominantly sequential approach assessed in the SERAPHIN study, the rate of all-cause hospitalizations was significantly reduced in the group receiving macitentan 10 mg.[3] However, this effect was mainly achieved by a reduction in PAH-related hospitalizations. These findings illustrate that patients with PAH present a high rate of non−PAH-related hospitalizations that have not been fully elucidated. It remains unknown whether treatment strategies for PAH have an impact on all-cause hospitalization and this could be addressed specifically in future studies.

An interesting finding in the current analysis is that 13% of patients in the pooled monotherapy group had PAH-related hospitalizations during the first year of treatment, compared with 2% of patients in the combination group. This finding, combined with FC II patients on combination therapy not experiencing a single hospitalization for worsening PAH during the study, suggests that the earlier a patient receives combination therapy in the disease process, the lower the risk of PAH-related hospitalization. According to the number needed to treat analysis, it is estimated that, for every 9 patients treated with combination vs monotherapy, 1 PAH-related hospitalization could be prevented over the course of 1 year.

European Union treatment guidelines for PAH (2015) recommend the use of initial monotherapy or initial combination therapy with equal weight for patients who are FC II or III.[5] The rationale for initial combination therapy to improve long-term outcomes is based on the fact that PAH is a multipathway disease. Previous studies using this approach were limited by their small samples sizes[6–8] and/or lack of a prospective control group.[7,8] In this study, among patients who had a PAH-related hospitalization, about one third (9 combination therapy, 14 monotherapy) did not experience this as the first clinical failure event. Thus, these patients may have been receiving a treatment different from their randomized therapy at the time of the PAH-related hospitalization. Country and center variations in terms of the threshold for hospital admission and the use of parenteral therapy may also have influenced the results. Whether any of the PAH-related hospitalizations due to initiation of parenteral prostanoid therapy were elective rather than emergent is unknown as data were not collected to address this in the AMBITION study.

In conclusion, in the AMBITION study, initial combination therapy with ambrisentan and tadalafil reduced the risk

of hospitalization for worsening PAH by 63% compared with pooled monotherapy, although the differences observed were not statistically significant in the post-hoc analysis of the rate of all-cause hospitalization between groups. Hospitalizations were mainly due to initiation of prostacyclin therapy and worsening of PAH. Post-hoc subgroup analysis suggested that the benefit was similar across the spectrum of PAH, irrespective of etiology of PAH, baseline WHO FC, baseline 6-minute walk distance, geographic region, sex, and baseline age. Post-hoc analysis also showed that pooled monotherapy, lower baseline 6-minute walk distance, and higher baseline NT-proBNP level were associated with an overall greater risk of hospitalization for worsening PAH.

Disclosure statement

J-L.V. has received institutional grants from Actelion and GlaxoSmithKline; speaker fees from Actelion, Bayer, GlaxoSmithKline, Pfizer, and Sonnivie; and advisory board honoraria from Actelion and Merck. N.G. has received grants and personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer. J.A.B. has received personal fees from Actelion, Bayer, and GlaxoSmithKline, and grants from Actelion, Bayer, GlaxoSmithKline, and Pfizer. A.E.F. has received funds for the conduct of the study from the Baylor College of Medicine; honoraria and travel/lodging expenses for being on the study's steering committee; grants from Actelion, Bayer, Gilead, and United Therapeutics; personal fees from Actelion, Bayer, Gilead, Ikaria, and United Therapeutics; and non-financial support from Bayer and Novartis. H.-A.G. has received grants from Actelion, Bayer, Novartis, and Pfizer; served as a board member and consultant for Actelion, Bayer, GlaxoSmithKline, Merck, Novartis, and Pfizer; and received payments for lectures from Actelion, Bayer, Novartis, and Pfizer. M.M.H. has received personal fees from Actelion, Bayer, Gilead, GlaxoSmithKline, Merck, and Pfizer. V.V.M. has received personal fees from Actelion, Bayer, Medtronic, St. Jude Medical, Steadymed, and United Therapeutics. A.J.P. has received grants and personal fees from Actelion, Bayer, Gilead, and GlaxoSmithKline, and personal fees from United Therapeutics. G.S. has received grants and personal fees from Actelion, Bayer, Gilead, and GlaxoSmithKline. C.B. is an employee of Gilead, and has stock options in Gilead. K.L.M., a former employee of Gilead, has received stock options from the company. J.L. is an employee of GlaxoSmithKline, and has received stock options in the company. L.J.R. has received consulting fees from Actelion, Arena, Gilead, and Karos.

This study was supported by Gilead Sciences, Inc., and GlaxoSmithKline. Statistical support was provided by Julia H.N. Harris, MA, of GlaxoSmithKline (Uxbridge, UK), and Hartington Statistics and Data Management, Ltd. Editorial support was provided by Michael S. McNamara, MS, of C4 MedSolutions, LLC (Yardley, PA), a CHC Group company. Monitoring and data collection for this study were performed or overseen by the sponsors. Statistical analysis was funded and overseen by the sponsors. Editorial support was funded by the sponsors.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.healun.2018.11.006.

References

1. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension (PAH) disease management (REVEAL). Chest 2015;148:1043-54.
2. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.
3. Channick RN, Delcroix M, Ghofrani HA, et al. Effect of macitentan on hospitalizations: results from the SERAPHIN trial. JACC Heart Fail 2015;3:1-8.
4. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
5. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.
6. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J 2004;24:353-9.
7. Kemp K, Savale L, O'Callaghan DS, et al. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: an observational study. J Heart Lung Transplant 2012;31:150-8.
8. Sitbon O, Jais X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J 2014;43:1691-7.
9. Ghofrani HA, Humbert M. The role of combination therapy in managing pulmonary arterial hypertension. Eur Respir Rev 2014;23:469-75.
10. Lajoie AC, Lauziere G, Lega JC, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. Lancet Respir Med 2016;4:291-305.
11. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44.
12. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the evaluation of medicinal products for cardiovascular disease prevention. London: European Medicines Agency; 2008.
13. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. London: European Medicines Agency; 2009.
14. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products for the treatment of acute heart failure. London: European Medicines Agency; 2015.
15. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
16. Farber HW, Miller DP, McGoon MD, et al. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. J Heart Lung Transplant 2015;34:362-8.

17. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015; 373:2522-33.
18. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J 2015;46:405-13.
19. Vachiery JL, Rubin LJ. Navigating the uncharted waters of combination therapy in pulmonary arterial hypertension: COMPASS or dead-reckoning. Eur Respir J 2015;46:297-8.
20. Burke JP, Hunsche E, Regulier E, et al. Characterizing pulmonary hypertension-related hospitalization costs among Medicare Advantage or commercially insured patients with pulmonary arterial hypertension: a retrospective database study. Am J Manag Care 2015;21(suppl):s47-58.
21. Burger CD, Long PK, Shah MR, et al. Characterization of first-time hospitalizations in patients with newly diagnosed pulmonary arterial hypertension in the REVEAL registry. Chest 2014;146:1263-73.
22. Savarese G, Musella F, D'Amore C, et al. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. Eur Respir J 2013;42:414-24.
23. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012;60:1192-201.