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Does Treatment Response to Ambrisentan Vary by Pulmonary Arterial Hypertension Severity? Implications for Clinicians and for the Design of Future Clinical Trials

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Abstract

Background—Recent clinical trials in pulmonary arterial hypertension have included World Health Organization (WHO) functional classes I–II patients. However, the impact of baseline functional class and other measures of severity on outcomes has not been evaluated in detail.

Methods—Outcomes at 12-weeks for patients grouped by functional class, hemodynamics, BNP level and six minute walk distance (6MWD) were evaluated for patients in the ARIES-1 and 2 pivotal trials of ambrisentan, a once daily oral endothelin-1 antagonist. Long-term outcomes in the ARIES-E extension study were also evaluated.

Results—At 12-weeks, ambrisentan treated patients with both early and late functional class showed similar improvement in 6MWD relative to placebo. However, patients with more severe disease tended to have greater improvement in 6MWD after grouping by other measures of severity. This included higher baseline BNP level, shorter baseline 6MWD and more severe baseline hemodynamics ($p < 0.05$ for BNP and $p = \text{NS}$ for other comparisons, analyzed as interaction terms). During long-term open label follow-up, maintenance of 6MWD improvement, freedom from clinical worsening and survival were also numerically worse for patients who were functional class III/IV at baseline.

Conclusions—Patients with both less severe and more severe PAH benefited from ambrisentan therapy vs. placebo in 12-week clinical trials and during long-term follow-up, but greater improvement vs. placebo was seen for those with higher BNP levels.

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Author Contributions:

Dr. K Chin contributed to the concept, design and analysis, wrote the first draft, contributed to revisions of the paper and assumes responsibility for the manuscript in its entirety.

Dr. S. Bartolome contributed to analysis and interpretation of the results and to critical revisions of the paper.

Dr. F Torres contributed to the concept and analysis and critical revisions of the paper.

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Introduction

Current treatment algorithms in pulmonary arterial hypertension (PAH) emphasize the need to identify and treat patients with PAH at the earliest time-point possible. However, differences in response to therapy by PAH severity are not well defined, because early functional class (class I/II) patients were excluded from many early clinical trials [1–5] and because sub-group analyses by PAH severity were generally limited in the clinical trials that did include earlier functional class patients [6–9]. Further evaluation is important both clinically and from the standpoint of future clinical trial design. In this paper, we sought to explore changes in 6MWD, BNP level and clinical worsening for patients treated with ambrisentan (Letairis®, Gilead, Foster City) vs. placebo in the 12-week ARIES-1 and ARIES-2 studies and in the long-term ARIES-E study. This patient population is ideal for this analysis, because comprehensive baseline information was obtained at study entry including functional class, BNP level, six minute walk distance (6MWD) and hemodynamics, and because large numbers of earlier functional class patients were enrolled. Additionally, the follow-up data in the ARIES-E provides an opportunity to evaluate longer-term outcomes.

Methods

Patient population

ARIES 1 and 2 were randomized placebo controlled clinical trials evaluating ambrisentan vs. placebo in PAH followed by ARIES-E, a long-term open label extension study. Methods and results were published in 2008 and 2009 by Galie *et al* [10] and Oudiz *et al* [11]. Briefly, patients with idiopathic PAH (IPAH) and PAH related to connective tissue diseases, HIV and anorexigen use with a baseline walk distance between 150 and 450 meters were randomized to 12-weeks of placebo, ambrisentan 5 mg or ambrisentan 10 mg in ARIES 1, and to placebo, 2.5 mg or 5 mg in ARIES-2. Patients completing the 12-week studies were eligible to enter the long-term extension. The studies were conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees provided approval of the protocols, and written informed consent was obtained from all patients.

For this paper, the analysis population included all subjects who were randomized to placebo, ambrisentan 5 mg, or ambrisentan 10 mg and received at least one dose of study medication in the ARIES 1 or 2 studies. Patients randomized to the 2.5 mg ambrisentan (N=65) were excluded because this dose has not been approved in the European Union or United States. Subjects were analyzed in the treatment group to which they were randomized.

PAH Severity: Subgroups Evaluated

Patients were grouped by four different markers of severity: functional class (I/II, III/IV), baseline 6MWD (≤ 350 m, 351–400 m, > 400 m), baseline hemodynamics (low risk: right atrial pressure (RAP) < 8 mmHg and cardiac index (CI) > 2.4 L/min/m², medium risk: RAP 8–15 mmHg and/or CI 2.1–2.4 L/min/m², high risk: RAP > 15 mmHg and/or CI ≤ 2

L/min/m²), and baseline BNP (<130 ng/L, ≥130 ng/L)³. [12] For the hemodynamics subgroup, subjects with RAP <8 mmHg and missing CI or subjects with CI 2.1–2.4 L/min/m² and missing RAP were included in the low risk subgroup. The functional class and hemodynamic cutoffs were chosen based on the 2009 ESC / ERS guidelines (table 15, parameters with established importance for assessing disease severity) [12]. The good / bad walk distance cutoffs in the ESC / ERS (>500 meters and <300 meters) could not be used because the maximum baseline walk distance allowed in the ARIES studies was 450 meters and because most patients had walk distances between 300 and 450 meters. We therefore included a >400 meter group, chosen based on the 2009 AHA / ACCF guidelines (Table 2: PAH: Determinants of Prognosis, better prognosis is >400 meters) [13], and we divided the remaining patients into a 351–400 meter and ≤350 meter groups. Finally, for BNP level, the guidelines do not provide a specific cutoff. As such, we chose to compare patients above vs. those below the median BNP level (130 pg / ml) in the ARIES data set. The evaluation of outcomes by functional class was prespecified in the original ARIES data analysis plans, while the hemodynamic, walk distance and BNP cutoffs were chosen post-hoc based on the criteria above.

Endpoints evaluated in this paper included change at 12 weeks in BNP level and 6MWD (ambrisentan vs. placebo), clinical worsening over 12 weeks (ambrisentan and placebo), and 6MWD, clinical worsening and survival over two years (open label ambrisentan).

ARIES-1 and ARIES-2: Subgroup Analysis

Baseline characteristics are presented using mean ± SD or percentages, except for BNP which is presented using the geometric mean with 95% confidence intervals. Analyses for all endpoints (6MWD, clinical worsening, survival) were performed separately for WHO functional class I/II and WHO functional class III/IV. Additionally, interactions between treatment (placebo, 5+10 mg ambrisentan) and each of the 4 PAH severity subgroup categories with respect to the change in 6MWD at Week 12 were examined using analysis of variance.

Change in 6MWD at 12 weeks was tested between treatment groups using the Wilcoxon rank sum test, stratified by IPAH and non-IPAH subjects and by study. Results are presented as both observed case (with no imputation) and as last observation carried forward (LOCF). For subjects who prematurely discontinued from the study for reasons of clinical worsening of PAH without a premature discontinuation assessment, “0” was imputed for 6MWD. Ninety-five percent confidence intervals for change in walk-distance were calculated using the mean square error obtained from analysis of variance.

BNP values were log-transformed, and change from baseline in log-transformed values were tested between treatment groups using the Wilcoxon rank sum test. Time to clinical worsening was defined as the time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study discontinuation due to the addition of other PAH therapeutic agents, or study discontinuation due to 2 or more early escape criteria. Kaplan-Meier event-free curves are presented, and differences between treatment groups were tested using the log-rank statistic.

Long-term treatment (ARIES-E)

Patients randomized to 5 mg or 10 mg initially were evaluated together because dosing was allowed to change after 24 weeks. Baseline was defined as the start of ambrisentan therapy.

Clinical worsening was evaluated using the above definitions. Subjects without events within 2 years were censored at study discontinuation or at the maximum of two years. Kaplan-Meier event-free curves by baseline functional class are presented with 95% confidence intervals around the point estimates. Survival time was the time from first ambrisentan dose to death with surviving subjects censored at the maximum of two years or study discontinuation. Kaplan-Meier survival curves are presented with 95% confidence intervals around the point estimates. Additionally, expected survival at 1, 1.5, and 2 years was calculated for each IPAH subject using the NIH formula⁴ [14] and, separately using the pulmonary hypertension connection (PHC) formula⁵. [15] Mean expected survival was presented graphically at each time point, along with the Kaplan-Meier estimates.

Results

Baseline characteristics

Of the 329 patients evaluated in the current analysis, most patients were functional class II (N=117) or functional class III (N=187) at baseline, while eight patients had functional class I symptoms and 17 patients had functional class IV symptoms. Patients with higher functional classes had lower 6MWD and more severe abnormalities in hemodynamics and BNP levels, but there were no clear differences in age, gender, race or etiology (table I).

12-Week Change in Walk Distance

Walk distance improvements for ambrisentan treated patients grouped by functional class were similar to the overall study results: functional class I/II patients had a 48.4 meter improvement vs. placebo, and functional class III/IV patients had a 46.8 meter improvement vs. placebo (combined 5 and 10 mg ambrisentan results; figure 1). In contrast, greater improvement in 6MWD vs. placebo was seen after grouping by other baseline measures of more advanced disease severity including hemodynamics, baseline walk distance and BNP level, and the comparison after grouping by BNP level was statistically significant (figure 2, $p<0.05$ testing BNP as an interaction term). As seen in figure 2, the net improvement in 6MWD depended not just on how well the ambrisentan treated patients responded to therapy, but also on whether the placebo treated patients had a significant *decline* in their walk distances. For example, ambrisentan treated patients with a BNP level ≥ 130 pg/ml improved 37.5 meters vs. baseline (combined 5 and 10 mg ambrisentan doses), but their “placebo-corrected” improvement was 72.0 meters because the placebo group lost 34.5 meters.

12-Week Change in BNP Level and Functional Class

BNP levels were lower in functional class I/II patients at baseline compared with functional class III/IV patients. After 12-weeks of therapy, both groups showed improvement vs. baseline ($p<0.05$ for both groups, figure 3). Changes in functional class from baseline to 12 weeks are shown in figure 4; this was not evaluated statistically.

Clinical worsening at 12 Weeks

Clinical worsening events during the 12 week placebo controlled study were uncommon among functional class I/II patients, with only 3 events (6%) in patients randomized to placebo and no events in patients randomized to ambrisentan ($p=NS$, figure 5). In contrast, functional class III/IV patients experienced more events overall and the clinical worsening event rate was higher among placebo treated patients (17 of 81, 17%) compared with ambrisentan treated patients (9 of 123, 7.3%, $p<0.05$).

2-year extension: survival and clinical worsening

Patients who were functional class I/II at the time of initiation of ambrisentan had generally favorable outcomes. This included a sustained approximately 40 meter improvement in 6MWD over two years seen in both observed cases and last observation carried forward analyses (figure 6) as well as high rates of freedom from clinical worsening (table II and figure 7). Survival was 95% and 92% at one and two years, respectively (figure 8).

Outcomes were not as favorable for functional class III and IV patients: looking *only* at the patients who completed a 6MWD at each time point ("observed cases"), an approximately 40 meter improvement in 6MWD was seen throughout. However, when evaluated using the more conservative last observation carried forward analysis, a drop-off in 6MWD is seen at one and two years. Freedom from clinical worsening was also lower, with just 76% and 61% of the functional class III/IV patients having no event at one and two years, respectively. Survival was 90% at one year and 83% at two years.

In order to put the survival data into perspective, we also compared long-term survival vs. predicted survival using the NIH registry equation and the more recently published PHC equation among the subset of ARIES-1 and ARIES-2 patients who had IPAH. The NIH registry population consisted of patients treated prior to the development of PAH-specific therapies, while the PHC equation was derived in the modern era. In the overall group, survival was better than that predicted by the NIH equation and similar to predicted survival based on the PHC equation. After grouping by functional class, patients with functional class I/II symptoms had survival rates that were slightly better than predicted by their hemodynamics alone using the PHC equation (figure 9), while class III/IV patients had survival rates similar to what their hemodynamics alone would predict. For reference, 80% of patients in the PHC population were functional class III/IV.

Discussion

In this analysis of the ARIES 1 and 2 data, patients with both less severe and more severe disease showed improvement in 6MWD with ambrisentan treatment, but there was some heterogeneity. In particular, patients with more advanced disease by several measures had numerically greater improvement in 6MWD, and this was statistically significant for those with BNP levels above the median value vs. those with BNP levels below the median. The other important finding in the study was that while most patients maintained their improvement in 6MWD over the 2-year open label follow-up period, declines were seen in

some including particularly patients who were at a later functional class when therapy was initiated.

Clinical Trial Implications - 12-week 6MWD results

Although the change in 6MWD at 12-weeks was similar in patients with functional class I/II and functional class III / IV symptoms, improvement was numerically greater for patients with more severe disease, as defined by other baseline measures, including particularly BNP level. Six other studies have reported numerically greater improvement among patients with more advanced disease including later functional class, more severe hemodynamics and lower baseline 6MWD (figure 10). This has included both clinical trials that used so called ‘traditional’ inclusion-exclusion criteria (maximum baseline 6MWD 450 meters) [3, 6–8] and studies that allowed longer baseline 6MWD [9]. However, this is not seen universally, and in fact in one trial patients with less severe disease had greater improvement in 6MWD [16]. Our results as well as the majority of prior clinical trial results suggest that in a typical 12-week PAH trial with 6MWD as the primary endpoint, power *might* be increased by limiting enrolment to patients with more advanced disease.

Clinical Trial Implications - Other Study Designs

Many active or recently completed studies in PAH are “add-on” therapy trials, meaning that background PAH therapy is allowed or even required [17]. Primary end-points are usually 6MWD or clinical worsening, and longer study durations are becoming more common. The ARIES-E results are therefore interesting as they may provide insight into how a control group (continued monotherapy) might behave in a multi-year add-on therapy study. Overall, 6MWD results were generally stable, but declines were seen, particularly among functional class III/IV patients and after 6–12 months follow-up (figure 6). Clinical worsening rates were also higher in patients with more advanced baseline functional class. This suggests that add-on therapy studies may have greater power when utilizing a longer study duration and / or enrolling patients with more advanced disease.

Clinical Implications

Clinically, two important findings are noted. First, patients with more advanced disease who were randomized to placebo did poorly during the 12-week clinical trial. This is seen in their 17% clinical worsening rate (vs. 7.3% for those on ambrisentan) and in the decline in 6MWD vs. baseline for placebo group patients with more advanced disease (figure 2). These findings suggest that any delays in the diagnosis and initiation of therapy may be particularly deleterious for PAH patients with advanced disease.

The second important finding was that long-term, a higher clinical worsening and mortality rate was seen for functional class III/IV patients *in spite of* similar and significant early improvements in 6MWD, compared with functional class I/II patients. The key difference likely relates to post-treatment status: sicker patients who respond to therapy will often still be at high risk of later decompensation, particularly if key prognostic “thresholds” are not achieved. Survival studies have reported better outcomes when patients achieve a normal or near-normal BNP level, a normal RAP and CI, a 6MWD >380–440 meters, and functional class I/II symptoms. Further, achieving these thresholds seems to be more important than

achieving a certain percentage or magnitude of improvement [12, 18]. Therefore, although not directly investigated in this study, careful and early reassessment of response to initial therapy is required, even when patients are walking further and feeling better than baseline.

Finally, the discordance between the clinical recommendations and our recommendations for clinical trial design is worth noting: clinical trials may be more likely to be positive if sicker patients and / or longer placebo-controlled time periods are utilized. However, from a clinical standpoint, these are the type of patients and studies which create an ethical dilemma. Of course, one's duty, first and foremost, is to the individual patient. At the same time, novel therapies and combinations of therapies cannot be assumed to be effective until they are studied in randomized controlled clinical trials – requiring a careful balancing act for the physician-investigator.

Study limitations

This study is limited by small patient populations for the sub-groups, inherent problems in LOCF imputation used for missing data, the lack of a placebo control after 12 weeks, and the use of *post-hoc* analysis. In particular, individual sub-group results should be considered exploratory. Nevertheless, the general trends including greater effect-size in sicker PAH patients are worth further study in future clinical trials.

Conclusions

In summary, we found that ambrisentan treatment led to improvement in 6MWD after grouping patients by four different measures of baseline severity: functional class, 6MWD, hemodynamics and BNP. However, significant heterogeneity in the results was seen, including greater 6MWD improvement at 12 weeks among patients with higher baseline BNP levels. Longer-term, patients with functional class III/IV symptoms at diagnosis had worse outcomes than patients who were functional class I or II at diagnosis. These findings may be helpful in anticipating clinical outcomes for patients starting therapy with ambrisentan and in the design of future clinical trials in PAH.

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Conflicts of interest:

K Chin has served as an investigator in clinical trials for Actelion, Bayer, Geno, Gilead, Pfizer, and United Therapeutics and has received grant support from the NIH. She has served as a consultant for Actelion and Bayer.

Dr. S. Bartolome has received financial support for clinical research, advisory board, and/or speaker engagement from the following institution/industry: NIH, Gilead, Actelion, Pfizer, Glaxo Smith, Novartis, United Therapeutics, GeNO, and Bayer.

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K. Miller, C. Blair and H. Gillies are employees of Gilead Sciences

Abbreviations

6MWD	Six minute walk distance
ABS	Ambrisentan
ARIES	Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter Efficacy Study 1 and 2
BNP	Brain Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
IPAH	Idiopathic Pulmonary Arterial Hypertension
WHO	World Health Organization

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What's known?

Recent clinical trials have demonstrated that ambrisentan therapy is associated with long term improvements in exercise capacity and a low risk of clinical worsening and death in patients with pulmonary arterial hypertension.

What's new?

The impact of baseline functional class and other measures of severity on outcomes has not been evaluated in detail in previous trials. Patients with both less severe and more severe PAH benefited from ambrisentan therapy vs. placebo in 12-week clinical trials and during long-term follow-up, but greater improvement vs. placebo was seen for those with higher BNP levels.

A: Functional Class I/II

B: Functional Class III/IV

Figure 1.

A) 6MWD Change from Baseline: WHO Functional Class I and II by Dose

B) 6MWD Change from Baseline: WHO Functional Class III and IV by Dose

Figures: Patients receiving ambrisentan showed significant improvement in 6MWD vs. placebo, after grouping by functional class (I/II and III/IV). Values are Mean $\pm$ SEM.

Analysis is using last observation carried forward. * $p < 0.05$ § $p < 0.001$

Figure 2. Change from Baseline to Week 12 in 6MWD

Figure 3. Change in BNP Level From Baseline to 12-Weeks by WHO Functional Class
 Values are geometric mean $\pm$ SEM. * $p < 0.05$, § $p < 0.001$. P-values are from Student t-test comparing each active treatment to placebo. For each subject, $\log(\text{week 12 BNP})$ minus $\log(\text{baseline BNP})$ was calculated.

WHO FC I/II

WHO FC III/IV

Figure 4. Change from Baseline in WHO Functional Class by WHO Functional Class

At Risk:

FC I/II, Placebo:	n=51	n=51	n=51	n=50	n=49	n=49	n=39
FC III/IV, Placebo:	n=81	n=81	n=79	n=72	n=68	n=64	n=56
FC I/II, ABS:	n=74	n=74	n=74	n=73	n=73	n=73	n=60
FC III/IV, ABS:	n=123	n=122	n=119	n=115	n=113	n=112	n=91

Figure 5. Time to Clinical Worsening by WHO Functional Class in 12-Week Placebo Controlled Study

Clinical worsening at 12-weeks was highest in functional class III/IV patients randomized to placebo. WHO FC I/II: 5+10mg ambrisentan vs. placebo, $p=0.032$. WHO FC III/IV: 5+10mg ambrisentan vs. placebo, $p=0.005$

A: Observed Case

WHO FC I/II, n=123	112	108	100	96
WHO FC III/IV, n=164	138	120	112	104

B: LOCF

Figure 6. 6MWD Over Two Years by Baseline WHO Functional Class

Values are mean $\pm$ 95% confidence interval, 5mg + 10mg ABS combined. The initial improvement in 6MWD was maintained over two years follow-up for most patients.

However, using the more conservative last observation carried forward analysis (LOCF; panel B), some drop-off is observed particularly among the later functional class patients.

For the LOCF analysis, WHO I and II n=121; WHO III and IV, n=161; 5mg + 10mg ABS

Figure 7. Long-Term Clinical Worsening by WHO Functional Class

Clinical worsening rates were higher among patients with baseline functional class III/IV symptoms. Kaplan-Meier estimate (95% CI); clinical worsening = first occurrence of death, lung tx, PAH hospitalization, atrial septostomy, addition of prostanoid therapy, or study withdrawal due to addition of other PAH drugs

Figure 8. Long-Term Survival by WHO Functional Class: Kaplan Meier Curves

Figure 9. Long-term Survival in IPAH Subjects

Long-term survival in ARIES-E compared favorably with predicted survival based on hemodynamics. Values for ARIES are mean $\pm$ 95% CI; mean values are shown for NIH and the pulmonary hypertension connection (PHC) formula.

Figure 10. Walk Distance Improvement (Meters) in PAH Clinical Trials Among Patients with Less Severe and More Severe Disease

Functional class is I/II vs. III/IV. 6MWD and hemodynamic cutoffs varied. Distances shown are “placebo-corrected”, meaning difference in walk distance improvement for placebo vs. treatment groups. For studies where results for multiple doses were reported, the results for the U.S. FDA approved dose (sildenafil 20 mg tid, tadalafil 40 mg daily) are shown.

*Estimated from published graphs. Studies: Tadalafil (PHIRST): Barst *et al* 2011[6]; Sildenafil (SUPER): Galie *et al* 2005[7]; Treprostinil: Simonneau *et al* 2002[8];

Epoprostenol $\pm$ sildenafil (PACES): Simonneau *et al* 2008[16]. Bosentan (BREATHE-1): Rubin et al 2002[3].

Table 1
Baseline Demographic and Disease Characteristics by WHO Functional Class

Values are mean $\pm$ SD unless otherwise noted. For BNP, n=7 (FC I), n=103 (FC II), n=171 (FC III), and n=17 (FC IV)

Characteristic	FC I (N=8)	FC II (N=117)	FC III (N=125)	FC III (N=187)	FC IV (N=17)	FC III/IV (N=204)
Female sex, %	88	79	79	80	82	80
Age, y	50 ($\pm$ 18)	48 ($\pm$ 15)	48 ($\pm$ 15)	53 ($\pm$ 15)	44 ($\pm$ 16)	52 ($\pm$ 15)
Race, %						
Caucasian	75	73	73	76	82	77
Diagnosis, %						
Idiopathic PAH	88	56	58	67	71	67
Associated PAH						
CTD	13	39	37	30	12	29
HIV/Anorexigen	0	5	5	3	18	4
6MWD, m	383.1 (51)	375.9 (65)	376.3 (64)	331.4 (79)	246.3 (67)	324.3 (82)
BDI	1.3 (0.9)	3.0 (2.0)	2.9 (1.9)	4.3 (2.1)	5.1 (2.7)	4.4 (2.1)
Mean PAP, mmHg	43 (14)	47 (15)	46 (15)	51 (13)	61 (16)	52 (13)
Cardiac index, L/min/m ²	2.6 (0.9)	2.8 (0.8)	2.8 (0.8)	2.3 (0.7)	2.4 (0.9)	2.3 (0.7)
PVR, mmHg/L/min	9.9 (6.4)	9.2 (6.2)	9.3 (6.2)	12.1 (6.7)	16.7 (5.8)	12.5 (6.7)
Mean RAP, mmHg	5.9 (3.4)	7.0 (4.2)	6.9 (4.2)	8.7 (5.3)	12.4 (6.9)	8.9 (5.5)
BNP, ng/L (geo. mean, 95% CI)	74.2 (20.6, 268.0)	67.7 (53.0, 86.5)	68.1 (53.7, 86.3)	156.3 (128.0, 191.0)	358.7 (207.6, 619.7)	168.5 (139.3, 203.9)

Table II
Clinical Worsening Events by WHO Functional Class

Clinical worsening events observed over two years during ARIES-E.

	WHO FC I/II	WHO FC III/IV
	5 mg + 10 mg (N=123)	5 mg + 10 mg (N=164)
Clinical worsening, %		
Death	4.1	14.6
Hospitalization for PAH	8.9	27.4
Withdrawal, other PAH treatment	0.8	1.8
Addition of prostacyclin analog therapy	4.9	12.8
Early escape	0.0	1.8