AMBRISENTAN RESPONSE IN CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION (CTD-PAH) – A SUBGROUP ANALYSIS OF THE ARIES-E CLINICAL TRIAL

Aryeh Fischer, Christopher P. Denton, Marco Matucci-Cerinic, Hunter Gillies, Christiana Blair, James Tislow, Steven D. Nathan

ABSTRACT:

Objective: Pulmonary arterial hypertension (PAH) is a condition which may lead to right ventricular failure and early mortality and is an important complication in patients with connective tissue disease (CTD). Previously, the endothelin A selective receptor antagonist, ambrisentan, has demonstrated efficacy and safety in treating patients with PAH due to a WHO Group I etiology. In this report, we describe the 3-year efficacy and safety of ambrisentan in patients with CTD associated PAH (CTD-PAH).

Methods: Patients with CTD-PAH participating in the ARIES-1 and -2 clinical trials and their long-term extension were evaluated. Efficacy evaluations including 6-minute walk distance (6MWD), clinical worsening, and survival were collected at routine study visits. Categorical (30m) breakpoints for 6MWD were evaluated and additional analyses were conducted to determine any relationship between 6MWD and survival.

Results: 124 patients with CTD-PAH were evaluated. Survival information at 3 years was available for 112 (90%) subjects; clinical worsening data was available for 68% of subjects at 3 years, and 6MWD results were available for 73%, 60%, and 44% of subjects at 1-, 2-, and 3-years, respectively. 62.6%, 57.3%, and 58.2% of CTD-PAH patients treated with ambrisentan exhibited increases in 6MWD at 1-, 2-, and 3- years respectively. At 3 years, 64% of patients were free from clinical worsening and 76% of patients were still alive (Kaplan-Meier estimates). Factors with prognostic relevance included: improving 6MWD ≥ 30m over the first 12 weeks of treatment, the most recent 6MWD, and a 6MWD absolute threshold of 222m.

Conclusion: These analyses of the 3-year treatment of CTD-PAH patients with ambrisentan revealed improved clinical worsening and survival compared to historical controls. Furthermore, several key exercise parameters were identified which appear important in guiding individual patient treatment.

Key Indexing Terms:

AMBRISENTAN PULMONARY HYPERTENSION CONNECTIVE TISSUE DISEASES OUTCOME ASSESSMENT

From the Division of Rheumatology, University of Colorado School of Medicine, Denver, Colorado, USA; Gilead Sciences, Inc., Foster City, California, USA; and The Inova Advanced Lung Disease, Lung Transplant, and Pulmonary Hypertension Programs, Falls Church, Virginia, USA.

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A. Fischer, MD, Division of Rheumatology, University of Colorado School of Medicine, Denver, CO; C.P. Denton, MD, Royal Free Hospital and UCL Division of Medicine, London, UK; M. Matucci-Cerinic, MD, Department of Experimental and Clinical Medicine, Division of Rheumatology AOUC, University of Florence, Florence, IT; H. Gillies, MD, at the time of writing of this manuscript was employed by Gilead Sciences, Inc., Foster City, CA; C. Blair, MSc, and J. Tislow, Pharm.D., Gilead Sciences, Inc., Foster City, CA; S.D. Nathan, MD, Director, Inova Advanced Lung Disease Program, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA.

Address reprint requests and correspondence to S.D. Nathan, Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, 3300 Gallows Road, Falls Church, VA 22042. E-mail: steven.nathan@inova.org

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is an important complication in patients with connective tissue disease (CTD). A systematic review has reported that the prevalence of CTD associated PAH (CTD-PAH) is estimated to be 13%[1]. Due to the diversity of pathologies amongst the different CTDs, varying rates of association with PAH have been observed. For example, prevalence estimates of PAH in patients with systemic sclerosis (SSc) are 13%, while prevalence estimates of PAH in patients with systemic lupus erythematosus (SLE) are only 3.34%[1]. United Kingdom registry data has further demonstrated that approximately 90% of the cases of CTD-PAH are associated with SSc (74%), mixed connective tissue disease (8%), or SLE (8%)[2].

Although both are classified within WHO Group I PAH, significant differences exist between characteristics of CTD-PAH and idiopathic pulmonary arterial hypertension (IPAH) populations. CTD-PAH patients are typically older, predominately female, and have less severe hemodynamic impairment; however, their 6-minute walk distance (6MWD) is generally lower and survival is typically worse[2,3,4]. Contemporary survival estimates report one- and three-year survival rates of 70-82% and 47-53% respectively[2,5], although this depends on the associated CTD[6].

The objective of this manuscript is to describe the clinical outcomes associated with the use of the endothelin A selective receptor antagonist (ERA) ambrisentan in patients with WHO Group 1 CTD-PAH through a series of pre-specified and post-hoc analyses from the combined (ARIES-C) 12-week, placebo-controlled ARIES-1 and ARIES-2 clinical trials and its open-label extension ARIES-E. Importantly, since mean changes in the 6MWD may pose challenges in evaluating disease severity and response to therapy in the CTD-PAH population[7,8,9], we sought to analyze changes in other clinically-relevant and complimentary markers such as categorical changes in 6MWD, functional class changes, and change in Borg Dyspnea Index (BDI). We further examined these markers' relationship to other long-term outcomes including clinical worsening events and mortality in CTD-PAH patients over 3 years.

METHODS

Patients with CTD-PAH who received at least one dose of ambrisentan as part of the ARIES-C (ARIES-1 identifier: NCT00423748; ARIES-2 identifier: NCT00423202) and/or ARIES-E (identifier: NCT00578786) clinical trials were included in the analysis. The diagnosis of CTD-PAH was made according to accepted guidelines[10,11]. Hemodynamically, patients were required to have a documented mean pulmonary artery pressure $\geq$ 25 mmHg, pulmonary vascular resistance (PVR) > 3 mmHg/L/min, and a pulmonary capillary wedge pressure or left ventricular end diastolic pressure $\leq$ 15 mmHg. Patients with a baseline 6MWD < 150 or >450 m were excluded as were patients with a total lung capacity (TLC) < 70% or a forced expiratory volume in 1 second (FEV_1) < 65% of predicted normal values[12].

Upon completion of the 12-week, double-blind, placebo-controlled ARIES-1 or ARIES-2 clinical trials patients were eligible to enroll in the long-term, open-label ARIES-E clinical trial. Patients randomized to receive ambrisentan during the ARIES-1 or ARIES-2 trials continued to receive ambrisentan at the same dose (ARIES-1: 5mg or 10mg once daily; ARIES-2: 2.5mg or 5mg once daily) upon enrollment into ARIES-

E. Patients receiving placebo during the ARIES-1 or ARIES-2 trials were randomized to receive ambrisentan during ARIES-E at one of the dosages available in the clinical trial from which the patient originally participated. ARIES-E was open-label; however subjects and investigators were blinded to dose for the first 24 weeks of treatment during which time a single (blinded) dosage reduction was permitted in the event of study drug intolerance. After 24 weeks, dosage adjustments were permitted at the discretion of the investigator. The study designs for ARIES-1, ARIES-2 and ARIES-E have been previously published[12,13].

Safety and efficacy were evaluated every 4 weeks during ARIES-C. In ARIES-E, safety and efficacy were assessed at weeks 4, 12, 16, 24, 36, 48, and at 24-week intervals thereafter. At each time point, efficacy was assessed through 6MWD, BDI, WHO Functional Class (WHO FC), survival, and clinical worsening events. For purposes of the ARIES-C trial, clinical worsening events were defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH therapeutic agents, or study withdrawal because of early escape. Early escape allowed patients, after a minimum of four weeks of blinded treatment, who met 2 or more pre-defined criteria during ARIES-C to discontinue the study prematurely for safety reasons. While the addition of prostanoid therapy resulted in study discontinuation in the ARIES-C trial; in ARIES-E, the addition of prostanoid therapy resulted in a clinical worsening event but not study discontinuation. Furthermore, in ARIES-E, since there was no placebo arm, early escape was not included in the clinical worsening criteria definition.

In addition to absolute changes, 6MWD was further evaluated based upon categorical breakpoints. A prior analysis has demonstrated that the minimal clinically important difference (MCID) for PAH is approximately 33m while the MCID for CTD-PAH patients is approximately 24 meters[14]. Additionally, a meta-analysis of PAH clinical trials found a 26m change in 6MWD to be a “true but modest” predictor of outcomes in treatment-naïve subjects[15]. Consequently, categorical breakpoints of 30m were selected as a conservative measure of response to therapy.

Survival status (dead, alive, or unknown) for all patients was collated. Following the reporting of the ARIES-E 2-year results[13], and after completion of the ARIES-E study and final study report in 2010, the sponsor collected additional 3-year survival status from patients previously categorized as “unknown”.

Similar evaluations of 6MWD, clinical worsening, and survival were also conducted for IPAH patients participating in ARIES-C and ARIES-E. Analyses of the IPAH subgroup are presented for appropriate context.

STATISTICAL ANALYSIS

The statistical analysis of the ARIES-C and ARIES-E clinical trials has been previously published[12,13]. Descriptive statistics were performed on the intent-to-treat population (all randomized subjects receiving at least one dose of study drug). As the dosage of ambrisentan could be varied during the ARIES-E trial, results were pooled across dosages. It was prespecified in both ARIES-C and ARIES-E, that missing efficacy data was to be imputed with the last observation carried forward (LOCF); additionally,

for ARIES-C, it was prespecified that if a patient discontinued the study because of clinical worsening and did not have a premature discontinuation visit, then a worst score was imputed. For reference, observed cases (Obs) for patients with evaluable data at each specified time point are also reported. Continuous variables are described as mean ± standard deviation and categorical variables as absolute frequencies and percentages. Kaplan-Meier estimates for survival and freedom from clinical worsening are reported as point estimates with 95% confidence intervals, and the log-rank test was used to compare Kaplan-Meier curves. Receiver operating characteristic (ROC) curves were generated to assess the accuracy of the most recent 6 to 12 month absolute value and change in 6MWD/ WHO FC as a predictor of death. Subjects had to be in the study for at least 6 months to qualify for this latter analysis. (ROC) curve analysis results are expressed using c-statistics. Statistical analysis was conducted using SAS® Version 8.2 or higher (SAS Institute, Inc, Cary, NC).

RESULTS

Formation of the study cohort:

Of the original 383 patients included in the ARIES-E analysis, 124 (32%) had been diagnosed with CTD-PAH; 81.5% with SSc spectrum (61.3% SSc, 20.2% mixed connective tissue disease), 14.5% systemic lupus erythematosus, and 4% overlap syndrome. During the 12-week placebo-controlled ARIES-C study, 81 of the 124 CTD-PAH patients were randomized to receive ambrisentan [10mg (n = 22), 5mg (n = 40), 2.5mg (n = 19)] and 43 patients were randomized to receive placebo. Of the 251 IPAH patients randomized in the ARIES-C study, 10 placebo subjects were not eligible to enroll into the ARIES-E study, resulting in 241 IPAH patients included in the ARIES-E analysis. The disposition of the CTD-PAH study cohort is displayed in Table 1.

Clinical characteristics of the cohort:

Comparisons of the demographics of the CTD-PAH and IPAH populations are presented in Table 2. As has been previously published and consistent with registry data[3], patients in the ARIES-C and ARIES-E clinical trials with CTD-PAH were older, had shorter 6MWD, and had less severe hemodynamics than IPAH patients at baseline.

Monotherapy Status

As combination therapy with prostanoids was permitted during ARIES-E, the proportion of patients receiving ambrisentan monotherapy and combination therapy was evaluated. Concomitant, occasional PDE5 inhibitor therapy with sildenafil or vardenafil (tadalafil prohibited due to longer half-life) was permitted only for erectile dysfunction, however some subjects deviated from the protocol and started concomitant PDE5 inhibitor therapy for PAH during the study; administration of PDE5 inhibitor therapy for PAH while participating in ARIES-E is also reported as combination therapy. Of the 96 patients continuing to participate in ARIES-E and continuing to receive ambrisentan at the end of year 1, 88 (92%) were receiving ambrisentan monotherapy. By the end of year 2, 68 of the 77 continuing patients (88%) were receiving ambrisentan monotherapy and by the end of year 3, 41 of the 49 continuing patients

(84%) were receiving ambrisentan monotherapy. Due to the long-term nature of the ARIES-E study, less than half of the original study population continued participation in the ARIES-E study through 3 years. Those study subjects discontinuing participation in ARIES-E consisted of patients transitioning to commercially available ambrisentan, enrolling into another ambrisentan extension study - ABS-LT (ABS-LT identifier: NCT00777920), or terminating participation due to adverse events, withdrawal of consent, lack of improvement, early escape (only available in ARIES-C), discretion of the study sponsor, or other reasons (Table 1). Of available agents used in combination with ambrisentan, the most commonly used class was PDE5 inhibitors followed by inhaled prostanoids and then intravenous prostanoids.

6MWD and BDI

6MWD results were available for 88% (109/124) of CTD-PAH subjects at 12 weeks and for73% (91/124), 60% (75/124), and 44% (55/124) of CTD-PAH subjects at 1-, 2-, and 3-years respectively. During ARIES-C, CTD-PAH patients randomized to receive either 5mg or 10mg of ambrisentan saw 6MWD improvements at 12 weeks of 17m and 22m respectively, while patients randomized to ambrisentan 2.5mg or placebo saw a decline of 7.7m and 6.4m respectively (LOCF and imputation, p = NS for each dose vs placebo). Observed values were +8m for placebo and +23m, +27m, and +35m for ambrisentan 2.5mg, 5mg, and 10mg respectively. Most subjects were still on their originally randomized dose at the 1, 2, and 3 year study time points. Treatment with ambrisentan in the open-label ARIES-E extension resulted in a +9.9 (± 80.9) m improvement in 6MWD from baseline in CTD-PAH patients at week 48 (LOCF). The magnitude of change had decreased by year 2 (+3.5 ± 89.6 m) and, by year 3 had fallen below baseline values (-5.1 ± 88.4 m). Observed case values were consistently greater than those seen using LOCF with 6MWD changes of +13.3 ± 82 m, +16.7 ± 82.5 m, and +3.5 ± 84.1 m at 1-, 2-, and 3-years respectively. In contrast, the BDI improved with changes of 0.4, 0.4, and 0.1 at 1-, 2-, and 3-years, respectively (LOCF).

As previously described, efficacy parameters were also evaluated for IPAH patients in order to contextualize the changes seen with the CTD-PAH population. During ARIES-C, IPAH patients treated with ambrisentan 2.5mg (n=42), 5mg (n=83), and 10mg (n=41), demonstrated an improvement in 6MWD of +35.7m, +45.7m, and +50.6m, respectively, at 12 weeks (LOCF and imputation). IPAH patients receiving placebo (n=85) had a decrease in 6MWD of -13.4m at week 12 (LOCF and imputation). In the ARIES-E extension, IPAH patients treated with ambrisentan (n=238, no post-baseline values available for 3 patients) had changes in 6MWD of +38.2m, +28.7m, and +26.9m at 1-, 2-, and 3-years, respectively (LOCF).

A higher percentage of patients treated with ambrisentan demonstrated increases than those treated with placebo. At 12 weeks 71% (12/17) of patients treated with ambrisentan 2.5mg, 75% (27/36) of patients receiving 5mg, and 79% (15/19) of patients receiving 10mg had increases in their 6MWD while 57% (21/37) of placebo treated patients had an increase in their 6MWD (Obs). Furthermore, 53% (9/17), 42% (15/36), and 47% (9/19) of patients receiving 2.5mg, 5mg, and 10mg respectively, had improvements above the categorical threshold of 30m (Obs) while 32% (12/37) of placebo treated patients achieved this threshold (Figure 1a). Utilizing LOCF and imputation, 63% (12/19) of ambrisentan 2.5mg subjects, 73% (29/40) of ambrisentan 5mg subjects, 73% (16/22) of ambrisentan 10mg subjects,

and 51% (22/43) of placebo subjects achieved increases in 6MWD at 12 weeks. Long term, 63% (57/91), 57% (43/75), and 58% (32/55) of patients exhibited increases in 6MWD through 1, 2, and 3 years respectively (Obs) (Figure 1b). As mentioned previously, categorical breakpoints (in increments or decrements of 30m) were selected based upon the MCID established in other PAH analyses.

Functional Class status

Utilizing LOCF imputation, WHO FC was maintained or improved in the majority of patients at week 48 (90%, 109/121), year 2 (85%, 103/121) and year 3 (84%, 102/121) (LOCF, no post-baseline values available for 3 patients). WHO FC maintenance and improvement were also seen with observed cases with 92% (90/98) of patients demonstrating maintenance or improvement at 1 year, 89% (73/82) at 2 years, and 93% (57/61) at 3 years. Similarly, in the IPAH subgroup, WHO FC was maintained or improved in 91% (217/238) of patients at 1 year, 85% (203/238) at 2 years, and 87% (206/238) at 3 years (LOCF, no post-baseline values available for 3 patients).

Clinical worsening

Through the 3-year follow-up period 40 CTD-PAH subjects and 54 IPAH subjects were censored for this endpoint. The Kaplan-Meier estimates of time to clinical worsening in all CTD-PAH patients were similar to that observed in the IPAH patients. Event-free estimates at 1-year were 80% (95% CI: 72% to 87%), at 2-years were 71% (95% CI: 63% to 80%) and at 3-years were 64% (95% CI: 54% to 73%) in the CTD-PAH population and were 84% (95% CI: 79% to 89%), 71% (95% CI: 65% to 77%), and 63% (95% CI: 57% to 70%) over 1-, 2- and 3-years respectively in the IPAH population. The most frequent clinical worsening event observed was hospitalization for PAH which was seen in 23% of CTD-PAH patients through 3 years. This was followed by death (18%) and the addition of approved prostanoid therapy (11%). Other clinical worsening events were infrequent. The full Kaplan-Meier analysis – including data obtained beyond 3 years – did not show statistically significant differences in time to clinical worsening between CTD-PAH patients and IPAH patients ($p = 0.732$).

Survival

In the CTD-PAH population, Kaplan-Meier estimates of survival at 1-, 2-, and 3-years were 90% (95% CI: 85% to 95%), 80% (95% CI: 73% to 87%), and 76% (95% CI: 68% to 83%) respectively (Figure 2). The full survival analysis – including data obtained beyond 3 years – did show statistically significant differences in survival between CTD-PAH patients and IPAH patients ($p = 0.019$).

When evaluating the relationship between 6MWD and survival, patients with a change in 6MWD ≥ 30m at week 12 (n=47) demonstrated improved long-term survival compared to patients with either an improvement of < 30m or a decrease in 6MWD at week 12 (n=65) (Figure 3a, p=0.022). Interestingly, in patients with IPAH, Kaplan-Meier analysis did not reveal a relationship between the 6MWD changes at week 12 and long-term survival using these same thresholds (Figures 3b, p=0.673).

Receiver operating characteristic (ROC) analyses

Long-term ambrisentan in CTD-PAH

ROC analyses were performed in order to determine whether the most recent 6MWD was a predictor of death through 3 years and whether most recent WHO FC was a predictor of death through 3 years. ROC analysis of the most recent 6 to 12 month change in 6MWD prior to death showed a fair association (c statistic = 0.712) while the most recent absolute 6MWD demonstrated a good to excellent association (c statistic = 0.890) (Figure 4). Analysis of the most recent 6MWD ROC curve revealed 222m to have the highest sensitivity (0.9) and lowest fall-out (1 – specificity = 0.104). The positive predictive value of most recent 6MWD ≤ 222m was 53% and the negative predictive value of most recent 6MWD > 222m was 99%. Similarly, the most recent change in WHO FC prior to death showed a fair association with subsequent mortality (c statistic = 0.632) and the most recent WHO FC prior to death demonstrated an excellent association (c statistic = 0.906) (Figure 5).

Adverse events

Due to the three year duration of the follow-up, adverse events were common. The list of adverse events occurring with a frequency of at least 10% in the CTD-PAH study population can be found in Table 3. Adverse events with higher prevalence or of particular significance include peripheral edema (44%), anemia (23%), pulmonary hypertension (21%), arthralgia (20%), headache and upper respiratory infection (19% each), diarrhea (17.7%), and right ventricular failure (16.9%). In the CTD-PAH population, most cases of peripheral edema were mild to moderate in severity and none resulted in study discontinuation.

DISCUSSION

In this study we describe the clinical outcomes associated with the use of ambrisentan in patients with WHO Group 1 CTD-PAH through a series of pre-specified and post-hoc analyses from the combined (ARIES-C) 12-week, placebo-controlled ARIES-1 and ARIES-2 clinical trials and its open-label extension ARIES-E. Importantly, these analyses present, for the first time, the long-term efficacy and safety data associated with the use of ambrisentan in patients with CTD-PAH. The CTD-PAH patient group is phenotypically different from the IPAH group; therefore, this subgroup analysis of the ARIES-E open-label extension was conducted to determine the safety and efficacy of ambrisentan in this select group of patients.

The mean 6MWD values showed an increase at 1-year (+9.9m) which, by year 3, had decreased to below baseline (-5.1m). While these mean values include LOCF imputation where there was missing data, the categorical analysis only reflects observed cases and demonstrates that the majority of continuing subjects had improvements in 6MWD at 1-, 2-, and 3-years of treatment with many subjects achieving > 30m improvements. This suggests that the mean 6MWD of the CTD-PAH study population may not be as helpful as once thought as it underrepresents the changes which occur in significant subsets of patients. During the double-blind 12 week trial a number of placebo subjects also had categorical improvements in 6MWD; however, overall the number of subjects achieving improvements in walk distance was greater in the ambrisentan groups. The categorical analysis was further supported by the majority of patients who remained in the study maintaining or improving their WHO FC at each yearly

interval suggesting a disconnect between the mean reduction in 6MWD and the maintenance of or improvement in WHO FC.

The 6MWD is a measure that has traditionally been used as a surrogate to define clinical improvement in the PAH population and to follow the course of the disease. Furthermore, in the overall PAH population, the 6MWD has been a valuable method for evaluating functional response to therapy. However, while as an absolute measure it has been correlated with mortality in patients with IPF[16] and in patients with IPAH[17], it has not been validated in patients with CTD-PAH or, more specifically, SSc associated PAH[7,8,18]. It is known that patients with SSc have varying degrees of peripheral vascular disease, inflammatory muscle pain and weakness, and joint pain. It seems logical that these systemic contributions likely impact the ability of the 6MWD to accurately reflect the cardiopulmonary status in patients with CTD-PAH.

Clinical trials have historically focused on improvements in 6MWD as an efficacy parameter. However, two recent analyses demonstrated that improvement in 6MWD are not associated with improved short-term (3-4 month) outcomes[15,20]. A novel finding from our analyses of the ARIES-E CTD-PAH population is that short-term change in 6MWD might indeed have long-term prognostic implications for survival. As evidenced by the improved survival among patients with at least a 30m increase in 6MWD at week 12, this study reflects the importance of improving the 6MWD in the short term. Additionally, we have demonstrated the potential importance of maintaining 6MWD at or above an absolute value of 222m in this population. As demonstrated in the ROC analysis, a 6MWD ≤ 222m was associated with a positive predictive value of 53% for mortality while a 6MWD > 222m was associated with a negative predictive value of 99%. The results of these post-hoc analyses support the concept that aggressive therapy may be indicated in order to maximize the 6MWD early in the course of treatment and to maintain the improvement. Conversely, a precipitous decrease in 6MWD should warrant a thorough clinical evaluation and potentially timely intervention.

The concept of early and aggressive treatment has been substantiated through two recent clinical trials. The results of the Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension (AMBITION) study demonstrate that initial combination therapy with ambrisentan and tadalafil in newly diagnosed, treatment-naïve PAH patients with WHO Group I PAH results in a significant reduction in the risk of clinical failure events compared to initial monotherapy[21]. Specific to the CTD-PAH population, the Ambrisentan and Tadalafil Upfront Combination Thearapy in Scleroderma-Associated PAH (ATPAHSS) study demonstrated that upfront combination therapy with ambrisentan and tadalafil in treatment-naïve SSc-PAH patients significantly improved hemodynamics, RV structure and function, as well as functional status[22]. While our analyses reveal a majority of patients continuing in the study received monotherapy at each yearly interval, there were a substantial number of dropouts and patients receiving add-on therapy over the evaluation period. While there appears to be patients who do well on monotherapy long-term, there is no established method for predicting these patients. Consequently, early and aggressive treatment of CTD-PAH patients including initial combination therapy in an effort to maximize exercise capacity and survival may be prudent.

Long-term ambrisentan in CTD-PAH

Analysis of the full set of survival data – including those patients followed beyond 3-years – demonstrated statistically significant differences in long-term survival between the CTD-PAH population and the IPAH population. It is notable, however, that the Kaplan-Meier 3-year survival estimate of CTD-PAH patients was 76% which contrasts with the 3-year survival of 47 - 56% reported in the current therapeutic era[2,5,6,19,23].

The safety profile of ambrisentan throughout the 3-year ARIES-E clinical trial in CTD-PAH subjects was consistent with the observed profile from previous PAH clinical trials of ambrisentan[12,13]. Within this study population, peripheral edema was the adverse event occurring with the highest frequency but it did not result in any discontinuations of therapy.

There were several limitations to this analysis, the most substantial of which was patient drop-out. Over the 3-year treatment period, over half of the patients withdrew from the study with 49 of the original 124 patients evaluable and receiving ambrisentan at year 3 leading to potential selection bias. While the majority of patient drop-out was due to patients transitioning out of the study, large numbers of patients did discontinue due to other causes which might be more likely to impact the results. Consequently, results of these analyses should be viewed in this context. It should be noted that while there was a high number of patient drop-outs, the collection of long-term survival status was almost complete with survival status of 112 of the original 124 patients having been ascertained at year 3. As previously mentioned, ARIES-E was a voluntary open-label extension of a placebo-controlled clinical trial which could lead to responder bias. Additionally, randomization in the original ARIES-1 and ARIES-2 clinical trials and, consequently subsequent enrollment into ARIES-E was not stratified based upon the presence of CTD-PAH. Finally, due to the long-term nature of the ARIES-E study, prostanoids were available as add-on therapy at the discretion of the investigator and, while their initiation would have been captured as clinical worsening events, their use may have affected the long-term results reported. Similarly, while co-administration of PDE5 inhibitors was permitted only for erectile dysfunction, there were subjects who deviated from the protocol and started a PDE5 inhibitor for PAH during the study, and an impact upon study endpoints is possible.

CONCLUSION

The long-term clinical worsening in the CTD-PAH population from this study was similar to the IPAH study population and long-term survival – while worse than the IPAH study population - was improved over historical controls and registry data. While the mean change in 6MWD in the study population did show changes from baseline, categorical analysis using the MCID of 30m more accurately reflects improvements or deteriorations seen in large subsets of patients Furthermore, change in 6MWD over 12 weeks, as well as a 6MWD threshold of 222 meters were found to have prognostic relevance in this particular CTD-PAH population. Our analysis reflects the importance of early and aggressive treatment in order to maximize short-term improvement in 6MWD and, in an effort to achieve this, initial combination therapy should warrant consideration where appropriate. We suggest that future clinical trials should focus more on categorical changes in the 6MWD, but acknowledge that additional measures including patient-centered outcomes, evaluation of right ventricular function and other novel

endpoints should be explored further. Ultimately, the best endpoint for clinical trials might be composites which capture the global effects of the intervention on the disease. The implementation of such endpoints might require nuanced changes to best accommodate the CTD-PAH population.

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Table 1

Yearly Disposition of CTD-PAH patients (n = 124)[‡]

	1 year	2 year	3 year
Ongoing in study	96	77	51˜
Transitioned out of study*^	1	9	28
Terminated study*	27	38	45
Adverse event	15	23	27
Clinical status did not improve or deteriorated	3	3	3
Early escape[◊]	2	2	2
Voluntary withdrawal of consent	7	9	11
Discretion of sponsor	0	0	1
Other	0	1	1
Survival Status[¤]			
Alive	108	93	83
Dead*	12	24	29
Unknown*	4	7	12

[‡]Includes patients who participated in ARIES-1 or -2 but did not enroll into ARIES-E

***Yearly values are cumulative**

˜Includes 2 patients who discontinued treatment prior to 3 years but remained in study

^Most subjects who completed the extension study continued to receive ambrisentan either as a commercial product or as enrolled in another study.

◊Early escape was only available in ARIES-C

¤Includes data collected retrospectively for patients no longer participating in the study

Table 2

	Baseline Characteristics	
	CTD-PAH (n=124)	**IPAH (n = 241)**
Age, y	56 ± 13.3	49 ± 15.7
Female, n (%)	110 (88.7)	183 (75.9)
CTD Etiology, n (%)		
Systemic Sclerosis	76 (61.3)	n/a
SLE	18 (14.5)	n/a
Mixed CTD	25 (20.2)	n/a
Overlap Syndrome	5 (4)	n/a
6MWD, m	333 ± 88.2	353 ± 83.6
BNP, ng/L, mean (Q1, Q3)	328 (48, 365) (n = 113)	242 (50, 356) (n = 215)
Borg Dyspnea Index	4.0 ± 2.51	3.9 ± 2.3
WHO FC, n (%)		
I	2 (1.6)	10 (4.1)
II	57 (46.0)	96 (39.8)
III	56 (45.2)	117 (48.5
IV	9 (7.3)	18 (7.5)
mPAP, mmHg	42.8 ± 12.60 (n = 123)	52.4 ± 14.41
mRAP, mmHg	6.9 ± 4.03 (n = 121)	8.73 ± 5.42 (n = 235)
Cardiac Index, L/min/m^2	2.58 ± 0.75 (n=121)	2.41 ± 0.78 (n = 229)
PVR, mmHg/L/min	8.8 ± 5.82 (n = 121)	12.2 ± 6.61 (n = 232)
Years from PAH diagnosis	1.7 ± 3.53	2.2 ± 4.32

all values are mean ± SD unless otherwise stated

Baseline characteristics are the last available measurements collected prior to dosing of active study drug.

6MWD: 6-minute walking distance; BNP: B-type natriuretic peptide; CTD: connective tissue disease; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; CTD-PAH: connective tissue disease associated pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SD: standard deviation; SLE: Systemic Lupus Erythematosus; WHO FC: World Health Organization Functional Class

Table 3

Adverse events with an incidence of at least 10% in the CTD-PAH population over 3 years

Adverse Event	Combined ambrisentan (n = 124)
Peripheral edema	55 (44.4%)
Anemia	29 (23.4%)
Pulmonary hypertension	26 (21.0%)
Arthralgia	25 (20.2%)
Headache	24 (19.4%)
Upper respiratory tract infection	24 (19.4%)
Diarrhea	22 (17.7%)
Right ventricular failure	21 (16.9%)
Dyspnea exacerbated	20 (16.1%)
Cough	19 (15.3%)
Dizziness	18 (14.5%)
Palpitations	18 (14.5%)
Nausea	17 (13.7%)
Pain in extremity	17 (13.7%)
Dyspnea	16 (12.9%)
Nasopharyngitis	15 (12.1%)
Pneumonia	15 (12.1%)
Fatigue	14 (11.3%)
Urinary tract infection	14 (11.3%)

Figure 1a

Categorical Improvements in Exercise Capacity in CTD-PAH Patients Receiving Ambrisentan Over 12 Weeks

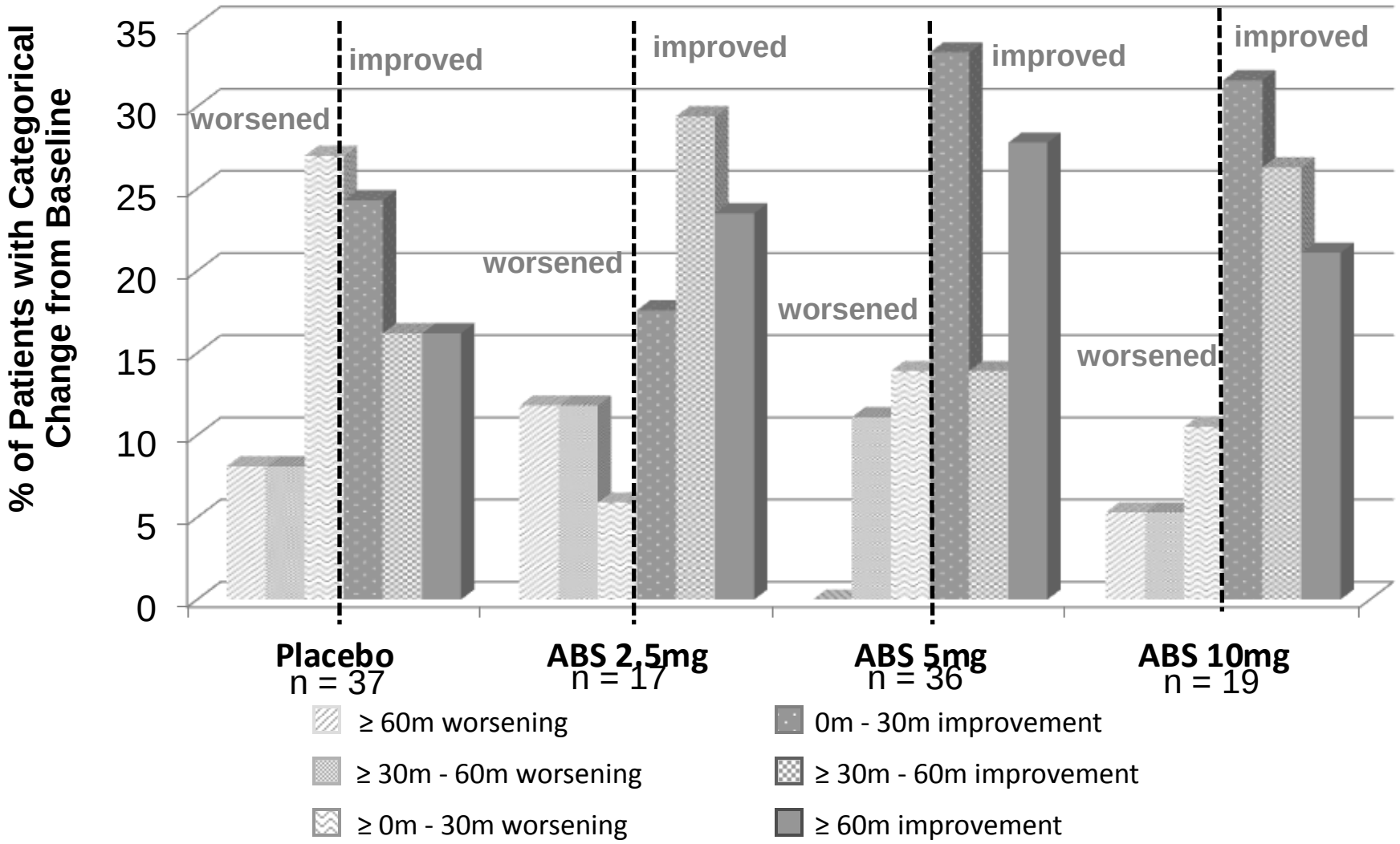
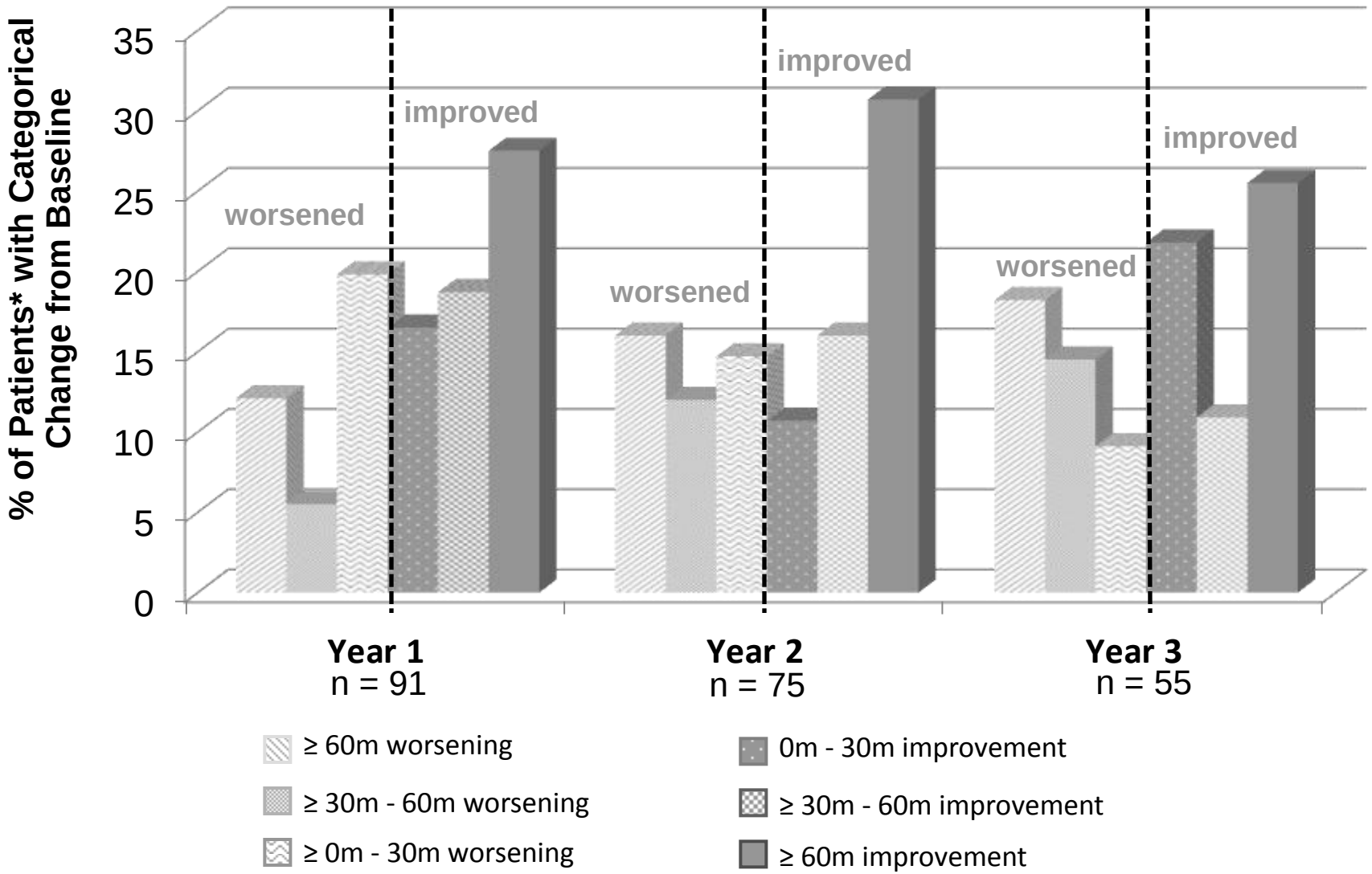


Figure does not include data for 10 patients who discontinued study (placebo = 4, ABS 2.5mg = 1, ABS 5mg = 3, ABS 10mg = 2), 3 patients who died (ABS 2.5mg = 1, ABS 5mg = 1, and ABS 10mg = 1), or 2 patients with missing values (placebo)

Figure 1b

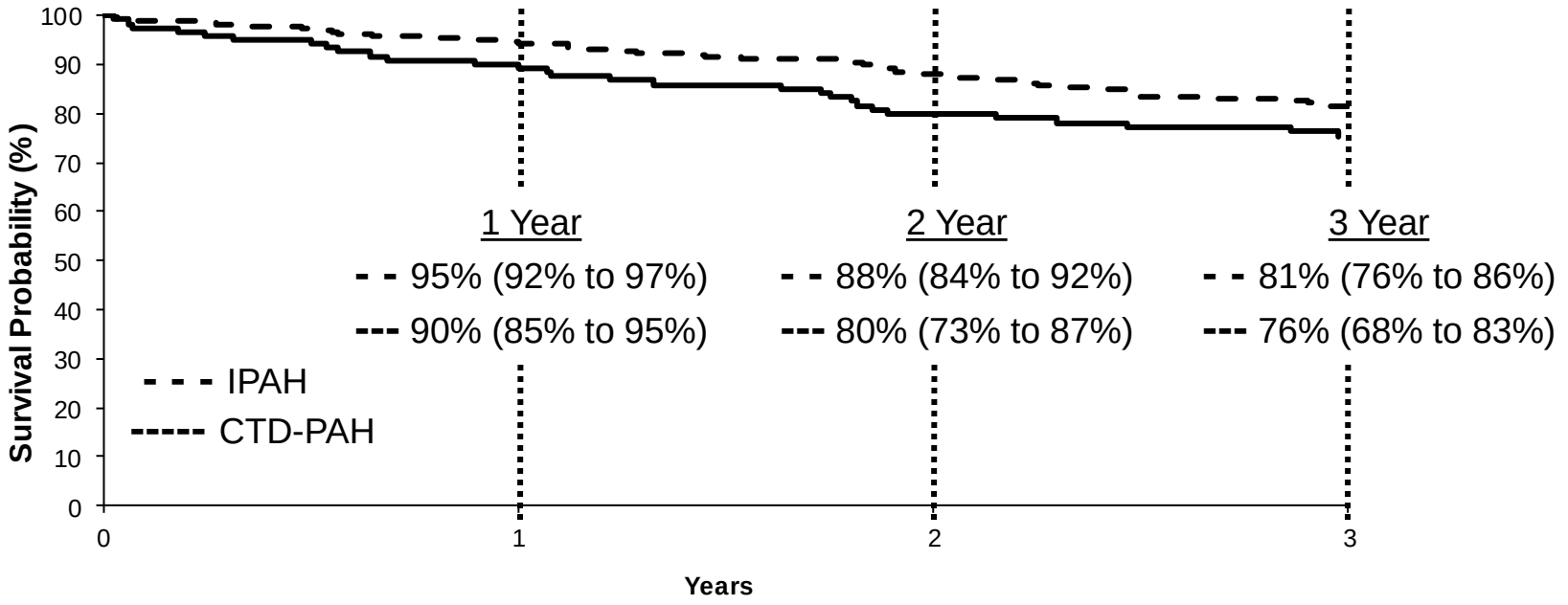
Categorical Improvements in Exercise Capacity in CTD-PAH Patients Receiving Ambrisentan Over 3 Years



*Percentages of patients are based upon the number of patients continuing in the study at each timepoint.

Figure 2

ARIES-E Survival Over 3 Years by Etiology

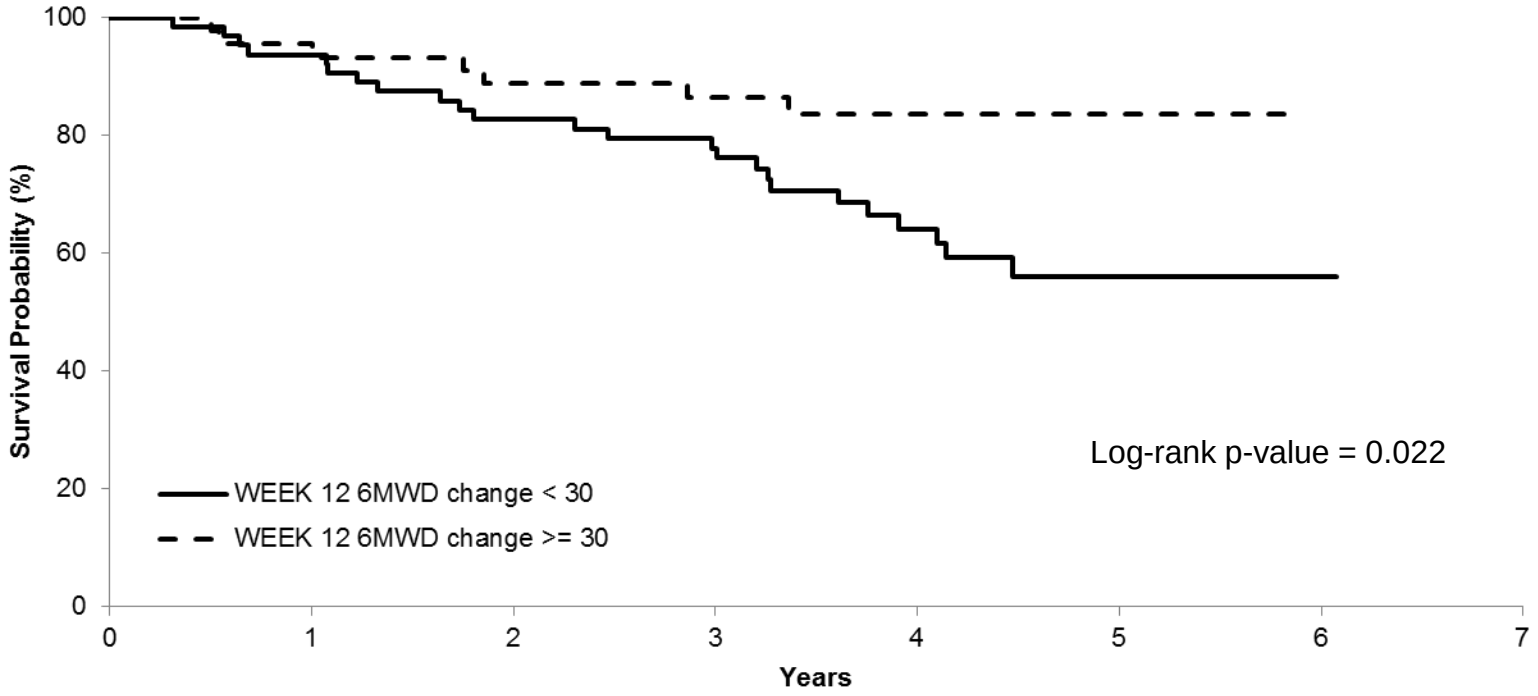


IPAH At Risk	n=241	n=226	n=209	n=187
CTD-PAH At Risk	n=124	n=108	n=93	n=83

Kaplan-Meier estimate (95% CI); Survival data includes vital status data collected after the end of the study.
p=0.019 for full survival analysis and includes data collected beyond 3 years and after the end of the study.

Figure 3a

ARIES-E Survival by Week 12 6MWD Change >= +30 m vs < +30 m CTD-PAH

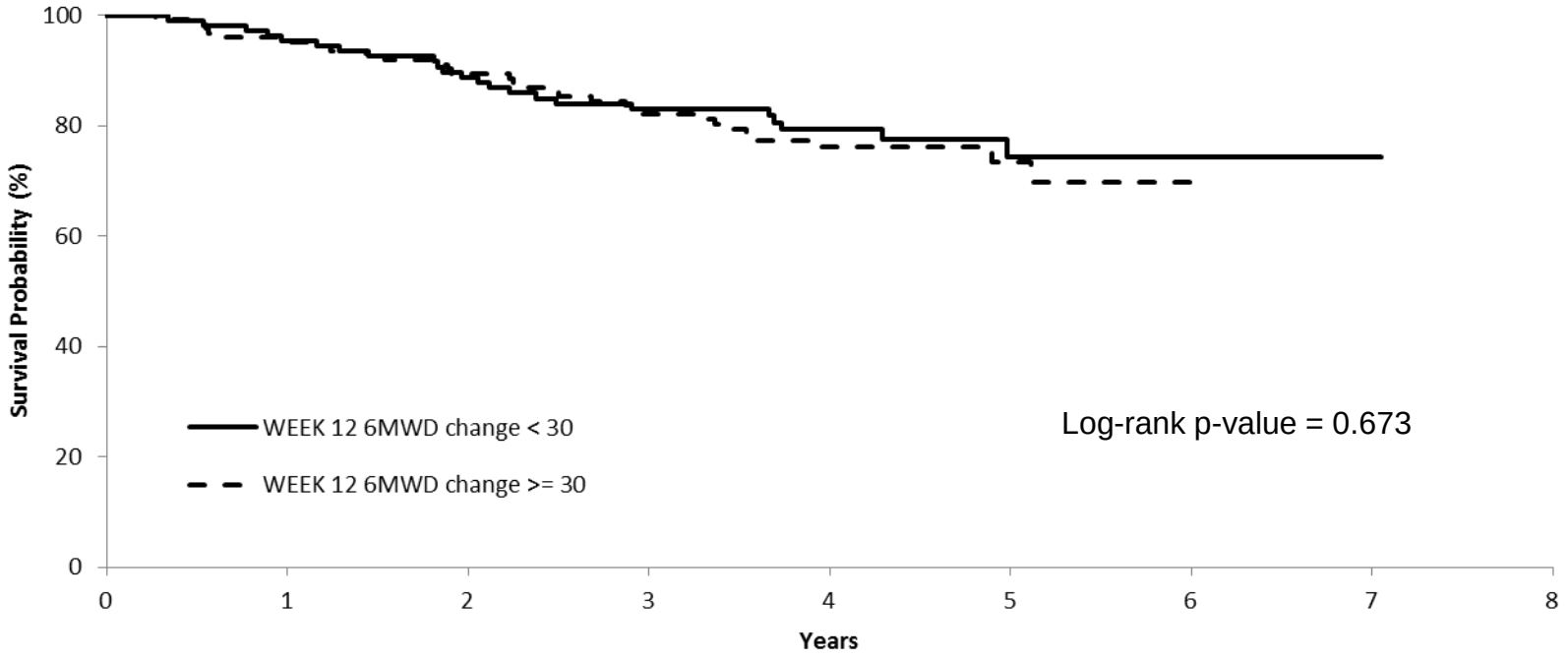


<30m								
At Risk	n=65	n=60	n=51	n=47	n=26	n=10	n=2	n=0
>=30m								
At Risk	n=47	n=43	n=40	n=35	n=22	n=9	n=0	n=0

Kaplan-Meier estimate (95% CI); Survival data includes vital status data collected after the end of the study.

Figure 3b

ARIES-E Survival by Week 12 6MWD Change >= +30 m vs < +30 m
IPAH



<30m								
At Risk	n=108	n=102	n=94	n=85	n=54	n=22	n=3	n=1
>=30m								
At Risk	n=124	n=118	n=109	n=97	n=68	n=23	n=2	n=0

Kaplan-Meier estimate (95% CI); Survival data includes vital status data collected after the end of the study.

Figure 4

ROC curves for Year 3 deaths in CTD-PAH subjects – Most recent 6MWD, Most recent change in 6MWD (N=87)

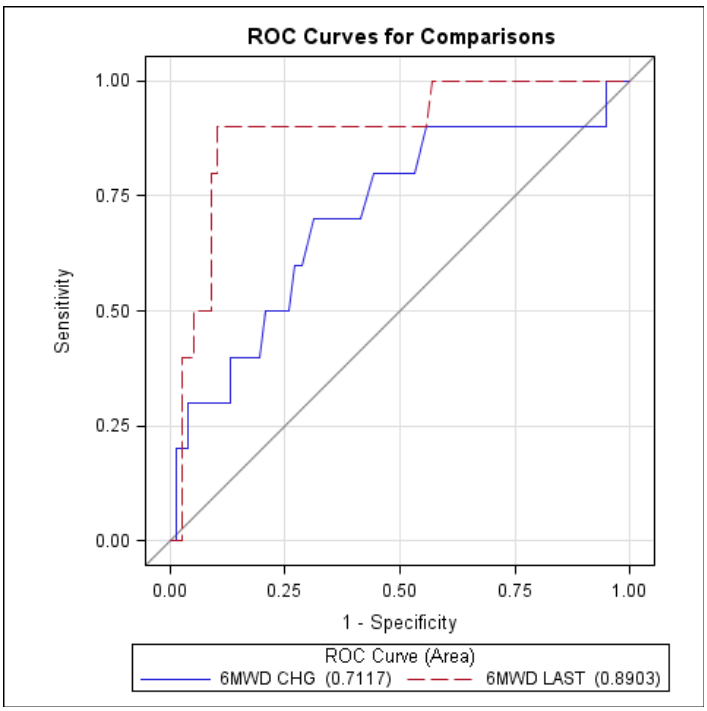


Figure 5

ROC curves for Year 3 deaths in CTD-PAH subjects – Most recent WHO, Most recent change in WHO (N=91)