Ambrisentan Therapy in Patients with Pulmonary Arterial Hypertension Who Discontinued Bosentan or Sitaxsentan Due to Liver Function Test Abnormalities


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Ambrisentan Therapy in Patients with Pulmonary Arterial Hypertension Who Discontinued Bosentan or Sitaxsentan Due to Liver Function Test Abnormalities

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Trial registry name: A Phase 2, Open-Label, Multicenter Study Evaluating Ambrisentan in Subjects With Pulmonary Arterial Hypertension Who Have Previously Discontinued Endothelin Receptor Antagonist Therapy Due to Serum Aminotransferase Abnormalities

Trial registration number: NCT00423592

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ABSTRACT

Background: Some endothelin receptor antagonists (ERAs) are associated with liver function test (LFT) abnormalities. However, ambrisentan has an incidence of serum aminotransferases >3 times the upper limit of normal (ULN) similar to that observed in PAH patients who are not taking ERAs. Because ambrisentan may provide benefits in PAH patients who have discontinued ERA therapy due to LFT abnormalities, we evaluated the safety and efficacy of ambrisentan in this patient population.

Methods: Patients who previously discontinued bosentan and/or sitaxsentan due to LFT abnormalities received ambrisentan at 2.5mg once daily for 4 weeks followed by 5mg for 8 weeks. The primary endpoint was the incidence of aminotransferases >3xULN considered by the investigator to be related to ambrisentan and resulted in drug discontinuation. Secondary endpoints included aminotransferases >5xULN requiring drug discontinuation and >3xULN requiring dose reduction, as well as changes in 6-minute walk distance (6MWD), Borg dyspnea index (BDI), WHO functional class, and SF-36® Health Survey score. Patients continued treatment beyond the 12-week endpoint with monthly monitoring of LFTs.

Results: Thirty-six patients who previously discontinued bosentan (n=31), sitaxsentan (n=2), or both (n=3) were enrolled. At baseline, 69.4% of patients were receiving prostanoid and/or sildenafil therapy. No patient had an aminotransferase >3xULN that required ambrisentan discontinuation. One patient had a transient aminotransferase >3xULN that resolved following a temporary dose reduction. No additional aminotransferases >3xULN were observed with long-term treatment (median exposure, 102 weeks), despite dose increases to 10 mg once daily in more than half of the patients. Significant improvements in 6MWD and other efficacy assessments were observed.
Conclusions: Ambrisentan treatment may be an option for patients who have discontinued bosentan and/or sitaxsentan therapy due to LFT abnormalities.

KEY WORDS

Ambrisentan, bosentan, pulmonary hypertension, endothelin receptor antagonist, hepatotoxicity, liver function test, propanoic acid, serum aminotransferase, sitaxsentan, sulfonamide
ABBREVIATION LIST

6MWD = 6-minute walk distance
ALT = Alanine aminotransferase
APAH = Associated PAH
AST = Aspartate aminotransferase
BID = Twice daily
BDI = Borg dyspnea index
CI = Confidence intervals
ET-1 = Endothelin-1
ERAs = Endothelin receptor antagonists
ET_A = Endothelin type A
ET_B = Endothelin type B
FPAH = Familial PAH
IPAH = Idiopathic PAH
ITT = Intent-to-treat
LFT = Liver function test
PAH = Pulmonary arterial hypertension
QD = Once daily
ULN = Upper limit of normal
WHO = World Health Organization
Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vasoconstriction, vascular smooth-muscle cell proliferation, and pathologic increases in pulmonary artery pressure and vascular resistance that usually lead to right ventricular failure and death. In idiopathic PAH, the median survival of untreated patients is 2.8 years, with a 34% survival rate at 5 years. Prognosis has improved with therapeutic advances, including the introduction of agents that target major pathways involved in the pathophysiology of PAH: endothelin, prostacyclin, and nitric oxide.

Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogen that mediates its effects through endothelin type A and B (ET\textsubscript{A} and ET\textsubscript{B}) receptors. Endothelin receptor antagonists (ERAs) are an important therapy for PAH, either as monotherapy or as a component of combination regimens. Bosentan (Tracleer; Actelion; Allschwil, Switzerland) is a sulfonamide-based, dual-receptor–selective (ET\textsubscript{A} and ET\textsubscript{B}) ERA that is approved for treatment of PAH. However, dose-dependent increases in liver aminotransferases were observed in a 16-week placebo-controlled study. At oral doses of 125 and 250mg twice daily (BID), 3% and 7% of patients developed hepatic aminotransferase concentrations >8 times the upper limit of normal (8xULN) and 4% and 14% developed hepatic aminotransferase concentrations >3xULN, respectively, necessitating dose reduction or discontinuation. Sitaxsentan (Thelin; Encysive; Houston, TX) is a sulfonamide-based ERA approved in the European Union and Canada for the treatment of PAH. Although sitaxsentan has similar efficacy outcomes to bosentan, there may be lower incidence of abnormal liver function tests (LFTs). In the STRIDE-2 (Sixtastantan To Relieve Impaired Exercise-2) trial, the 18-week incidence of elevated serum aminotransferase
concentrations >3xULN was 5% for sitaxsentan 50mg once daily (QD) and 3% for 100mg QD, compared to 11% for bosentan 125mg BID. A previous sitaxsentan trial that included a 300mg QD treatment arm demonstrated a dose-dependent increase in LFT abnormalities, limiting the therapeutic range of sitaxsentan to 100 mg QD. Furthermore, there have been reports of deaths related to fulminant drug-induced liver injury following sitaxsentan treatment. Patients treated with bosentan or sitaxsentan who experience abnormal LFTs are either discontinued from ERA therapy or may receive a lower, potentially subtherapeutic dose.

Ambrisentan (Letairis; Gilead; Foster City, CA) is an oral, once-daily, propanoic acid-based endothelin type A (ET\textsubscript{A}) receptor-selective ERA approved for treatment of PAH. Data from the initial dose-ranging study in patients with PAH suggested that ambrisentan may exhibit a low risk of aminotransferase abnormalities. This study was designed to determine the incidence of increased serum aminotransferase concentrations and the overall safety of ambrisentan in patients who had previously discontinued ERA therapy because of serum aminotransferase concentrations >3xULN.
METHODS

Patients

Patients 12 to 75 years of age with idiopathic PAH (IPAH), familial PAH (FPAH), or PAH associated (APAH) with connective tissue disease, congenital systemic-to-pulmonary shunts, anorexigen use, or human immunodeficiency virus (HIV) infection who had previously discontinued bosentan or sitaxsentan therapy, or both, due to serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) concentrations >3xULN (LFT abnormalities) were eligible for this study. Patients were required to have normal (<1xULN) serum aminotransferase concentrations and a 6-minute walk distance (6MWD) of ≥150 meters. Patients receiving sildenafil and/or a prostanoid (epoprostenol, treprostinil, iloprost) were required to have been on stable therapy for ≥4 weeks prior to screening. Females were required to have a negative pregnancy test, and to use a double method of contraception during and for at least 4 weeks following their participation. This multicenter study did not specifically require enrollment of all consecutively eligible patients.

Patients were not eligible if they had pulmonary hypertension due to coronary artery disease, left heart disease, interstitial lung disease, chronic obstructive pulmonary disease, veno-occlusive disease, chronic thrombotic and/or embolic disease, or sleep apnea; portopulmonary hypertension; portopulmonary hypertension; a total lung capacity <70% of predicted normal or forced expiratory volume in 1 second <65% of predicted normal; a hemoglobin concentration <10 g/dL or hematocrit <30%; or a resting arterial oxygen saturation <90% refractory to treatment with oxygen supplementation. All patients provided written informed consent.
Study Design

This was an open-label study conducted at 17 sites in the United States, Australia, and Europe. All patients in this case series received ambrisentan 2.5mg QD for 4 weeks before increasing to 5mg QD (Fig 1). After 12-weeks, patients could continue receiving ambrisentan treatment. After 24 weeks, investigators could adjust the ambrisentan dose as clinically indicated to 2.5, 5, or 10mg QD). Dose reduction was permitted at any time for ambrisentan intolerance, but was required if a patient had serum aminotransferase concentrations >3xULN and ≤5xULN. Discontinuation was permitted at any point based on the investigator’s judgment, regardless of serum aminotransferase levels; however, drug discontinuation was required if a patient had serum aminotransferase concentrations >5xULN. Concomitant treatment with sildenafil and/or prostanoids was permitted. This study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonisation.

Patient Assessments and Study Endpoints

The primary endpoint was the incidence of serum aminotransferase concentrations >3xULN that were assessed by the investigator to be related to ambrisentan and resulted in discontinuation of study drug during 12 weeks of therapy. Secondary safety endpoints included the incidence of serum aminotransferase concentrations >5xULN that were related to ambrisentan and required study drug discontinuation, and serum aminotransferase concentrations >3xULN that were related to ambrisentan and resulted in dose reduction. Secondary efficacy endpoints included change from baseline in 6MWD, Borg dyspnea index (BDI), World Health Organization (WHO) functional class, and quality of life measured by the SF-36® Health Survey.
All patients had blood drawn for LFTs and other clinical laboratory tests (including clinical chemistry, hematology, coagulation, urinalysis, and pregnancy) every 2 weeks during the first 12 weeks and every 4 weeks thereafter; more than 90% of all scheduled lab tests were collected. Efficacy assessments and other safety evaluations (e.g., adverse events, vital signs, and 12-lead electrocardiography) were performed every 4 weeks during the primary study period, every 12 weeks through week 48, and every 24 weeks thereafter.

Statistical Methods

All patients who received ≥1 dose of study drug constituted the safety population. Incidence of serum aminotransferase concentrations >3xULN was described by percentages and exact 2-sided 95% confidence intervals (CI) based on a binomial distribution. The intent-to-treat (ITT) population used for efficacy analyses consisted of patients who received at least 1 dose of study drug and had at least 1 post-baseline efficacy value. Missing efficacy data were imputed using the last observation carried forward. Change from baseline to week 12 in 6MWD, BDI, and SF-36® scores were summarized with descriptive statistics and were analyzed using a 2-sided 1-sample t-test to test the null hypothesis of no change from baseline after 12 weeks of therapy. Change from baseline in WHO functional class was summarized using frequencies and percentages of improvement from baseline (improved, no change, deteriorated), with no inferential statistics reported. No adjustment for multiple comparisons was made.
RESULTS

Study Population

Forty-two patients were screened for participation in the study and 6 patients failed screening: transaminase levels >1xULN (3 patients); inability to obtain baseline laboratory values (1 patient); lack of inclusion diagnosis (1 patient); and death (1 patient). A total of 36 patients were enrolled into the study between May and October 2005. Patient demographic and disease characteristics are summarized in Table 1. The majority were female (86.1%) and Caucasian (77.8%), and the population was slightly older than typically reported in previous PAH studies (mean age of 57 ± 13.4 years). Overall, 63.9% of the subjects had IPAH, 2.8% of subjects had FPAH, and 33.3% had APAH: 25.0% had PAH associated with connective tissue disease (mixed connective tissue disease, systemic lupus erythematosus, systemic sclerosis [scleroderma], overlap syndrome, CREST syndrome), 5.6% had PAH associated with congenital heart defects, and 2.8% had PAH associated with anorexigen use. All patients had WHO functional class II (36.1%) or III (63.9%) symptoms at baseline and most patients were receiving concomitant therapies (69.4%).

A summary of previous aminotransferase abnormalities is provided in Table 2. Most patients had previously discontinued bosentan therapy (n=31); 2 had discontinued sitaxsentan therapy and 3 had discontinued both ERAs. The majority of patients had previous experienced serum aminotransferase elevations >5xULN and 10 patients experienced elevations >8xULN. One patient receiving bosentan had elevations in ALT >3xULN and total bilirubin >2xULN, consistent with potential serious liver injury (Hy’s Law). The median duration of bosentan and sitaxsentan exposure prior to discontinuation of therapy was 13.9 and 28.7 weeks, respectively.
Additionally, 8 patients receiving bosentan and 1 receiving sitaxsentan had been re-challenged with their previous ERA; all 9 had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy.

Thirty-four patients completed the 12-week primary endpoint period and continued treatment in the extension period. The 2 patients who discontinued the study prior to week 12 experienced adverse events not related to LFT abnormalities (palpitations and extremity pain).

Ambrisentan Hepatic Safety

None (0%; 95% CI: 0.0% to 9.7%) of the 36 patients had a serum ALT or AST concentration >3xULN during 12 weeks of ambrisentan therapy which resulted in discontinuation of study drug (primary endpoint). One patient (2.8%; 95% CI: 0.1% to 14.5%) had a transient elevation in ALT concentration (3.2xULN) at week 12 that was considered related to ambrisentan treatment (secondary endpoint), but resolved following a temporary dose-reduction to 2.5mg. This patient was subsequently up-titrated to 5 and 10mg QD of ambrisentan with no further notable increases in serum aminotransferase concentrations during 8 months of additional treatment. No patient had a serum ALT or AST concentration >5xULN during 12 weeks of ambrisentan therapy.

Following the 12-week primary endpoint period, 34 patients received ambrisentan treatment. As of January 2008, median exposure was 102 weeks and maximum exposure was 119 weeks. Over half of the patients increased the dose to 10mg. As shown in Figure 2, no additional events of ALT or AST concentrations >3xULN occurred with long-term treatment.
Ambrisentan Safety and Tolerability

The most common adverse events (>2 patients) during the 12-week primary study were peripheral edema (n=9), headache (n=8), flushing (n=4), dyspepsia (n=3), dyspnea (n=3), nausea (n=3) and palpitations (n=3). Nearly all adverse events were reported as mild to moderate in severity, including all peripheral edema (which was treated effectively at the discretion of the investigator with added or increased doses of diuretics), headache, and flushing. A total of 28 (77.8%) subjects received diuretics during this study. Of these, 25 were receiving diuretics at baseline and 3 initiated a diuretic after the first dose of ambrisentan. Two (5.6%) patients experienced a serious adverse event, and one of these events (palpitations) resulted in study discontinuation. The second patient experienced anemia and elevated serum potassium that resolved without adjustment of study drug. One additional patient receiving concomitant epoprostenol discontinued the study after experiencing pain in an extremity. No clinically relevant changes in chemistry, hematology, vital signs, electrocardiogram parameters, or coagulation parameters were observed, except for mild reductions in mean hemoglobin concentration (-1.2 g/dL) and mean hematocrit (-4%).

Ambrisentan Efficacy

As shown in Figure 3A, improvement in exercise capacity (as measured by 6MWD) was observed at week 8 (+22 m; 95% CI: 6 to 38, \( p=0.010 \)) and was maintained at week 12 (+23 m; 95% CI: 6 to 40; \( p=0.009 \)). Similarly, decreased BDI (Figure 3B) was observed at week 8 (-0.8; 95% CI: -1.4 to -0.3; \( p=0.003 \)) and week 12 (-0.5; 95% CI: -1.0 to 0.0; \( p=0.046 \)). As shown in Figure 3C, there was a decrease in the percentage of patients with WHO class III symptoms and
an increase in the percentage with WHO class I symptoms associated with the use of ambrisentan. At week 12, 43% had an improvement in WHO class, 51% had no change in WHO class, and 6% had worsening WHO class compared to baseline. Significant improvements ($p<0.05$) were also observed for 6 of 8 domains in the SF-36® Health Survey (physical functioning, role-physical, general health, bodily pain scale, vitality, and mental health) and the composite physical health score (data not shown).
Although considerable progress has been made in developing new agents for treating patients with PAH, an unmet need remains for conveniently administered therapeutics with sustained safety profiles. In this context, an ongoing concern with ERAs is the potential for clinically significant and sometimes serious liver toxicity.

The mechanisms by which sulfonamide-based ERAs induce liver toxicity are not well established. Preclinical evidence suggests that elevations in aminotransferases observed with bosentan may result from inhibition of hepatocyte bile salt excretion and/or the uncoupling of lipid-bile salt secretion resulting in alterations of bile composition.\textsuperscript{11,12} In contrast, ambrisentan at concentrations ranging from 2 to 100 µM had no effect on bile salt export pump function, and little or no effect on other hepatic transporters compared with dose-dependent inhibition of these transporters incubated with bosentan or sitaxsentan.\textsuperscript{13} These data suggest a fundamental difference between ambrisentan and the sulfonamide-based ERAs regarding effects on hepatobiliary biology.

Overall, ambrisentan was well tolerated and the most frequently reported adverse events were consistent with ERA class effects.\textsuperscript{4,6,9} The hepatic safety profile was favorable, with no elevations in ALT or AST >3×ULN that required drug discontinuation. The only incident of serum aminotransferase concentration >3×ULN was mild, and the patient resumed and up-titrated ambrisentan to 10mg QD without abnormal LFT recurrence. These data were strengthened by the results from the extension period, in which the median duration of ambrisentan exposure was substantially greater than the exposure to bosentan or sitaxsentan therapy prior to the LFT event that led to drug discontinuation. Although edema was observed in
25% of the patients, the majority was receiving concomitant sildenafil and/or prostacyclin analogues at baseline and two-thirds were WHO class III at enrollment, reflecting a population with quite advanced disease and susceptible to peripheral edema. Nonetheless, all cases of peripheral edema were mild to moderate in severity and none of the events led to discontinuation of ambrisentan.

The lack of significant LFT abnormalities observed in this study is consistent with data from 2 large ambrisentan studies in patients with PAH (ARIES-1 and ARIES-2). In these studies, no patients receiving ambrisentan had serum ALT or AST concentrations >3xULN during the 12-week treatment period, with a 1-year risk of 2.8%. In retrospective analysis of the placebo arms of 4 large 12 to 18 week ERA trials, the incidence of abnormal LFTs was approximately 4%. These results suggest that the incidence of abnormal LFTs with ambrisentan is similar to expected background incidence in patients with PAH. It is interesting that other propanoic acid-based ERAs, such as darusentan and atrasentan, have also demonstrated a low potential for LFT abnormalities in several large randomized trials for hypertension, congestive heart failure, and prostate cancer. Further studies are required to investigate whether the low risk of abnormal LFTs associated with ambrisentan may be attributed to a lower daily dose (10mg versus 100mg and 250mg for sitaxsentan and bosentan, respectively) or differences in hepatobiliary interactions (e.g., transport proteins) that may be due to chemical dissimilarities among the ERAs.

Although the sample size was small and this study was not powered for efficacy assessment, patients did show improvement in exercise capacity, signs and symptoms of PAH, and quality of life. These results are consistent with the significant measures of efficacy in the placebo-controlled ARIES studies and are notable considering the high proportion of patients...
in this study who were receiving concomitant phosphodiesterase type 5 inhibitor or prostanoid therapy.

Conclusions based on this study are limited by small patient numbers and the lack of a placebo arm. Additionally, the primary endpoint was assessed after 12 weeks, which may not have been adequate time for hepatotoxicity development. However, the results from the first 12-weeks of treatment were maintained following more than 2 years of ambrisentan therapy.

Patients in this study initiated ambrisentan treatment at 2.5mg once daily for 4 weeks before the dose was uptitrated to 5mg daily, which may not be feasible or representative of clinical practice; only the 5 and 10mg doses have been approved for the treatment of PAH. However, no significant LFT abnormalities were observed in this study when the ambrisentan dose was increased to 5 and 10mg QD, suggesting that a 2.5mg lead-in period may not be necessary.

Finally, all patients had serum ALT and AST concentrations within normal limits prior to receiving their first dose of ambrisentan; therefore these data do not address a direct transition from other ERA therapies in patients with ongoing LFT abnormalities.

In conclusion, ambrisentan treatment was not associated with significant LFT abnormalities in an at-risk population who had previously discontinued bosentan or sitaxsentan due to elevated LFTs. Ambrisentan was well tolerated and improvements in several clinical parameters were observed. The use of ambrisentan therapy may be a viable treatment option for patients with PAH who have previously experienced liver abnormalities during bosentan or sitaxsentan therapy.

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FIGURE LEGENDS

FIGURE 1. Study design.

FIGURE 2. Kaplan-Meier curve of the time to first event. Time to first event is defined as alanine aminotransferase or aspartate aminotransferase level >3×ULN. Symbol (+) on the curve indicates the time at which subjects were censored.

FIGURE 3. Mean change from baseline in 6MWD (A), BDI (B), and WHO functional class (C). Error bars in 3A and 3B represent standard error of the mean.
Table 1—Demographic and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ambrisentan (N = 36)</th>
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<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>57 (13.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (86.1)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
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</tr>
<tr>
<td>Caucasian</td>
<td>28 (77.8)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>PAH Etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>23 (63.9)</td>
</tr>
<tr>
<td>FPAH</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>APAH</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>WHO functional class, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13 (36.1)</td>
</tr>
<tr>
<td>III</td>
<td>23 (63.9)</td>
</tr>
<tr>
<td>6MWD, m, mean (SD)</td>
<td>397 (105)</td>
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<tr>
<td>BDI, units, mean (SD)</td>
<td>4.2 (2.3)</td>
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<tr>
<td>PAH treatment, n (%)</td>
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</tr>
<tr>
<td>Ambrisentan alone</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Ambrisentan/sildenafil</td>
<td>12 (33.3)</td>
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<tr>
<td>Ambrisentan/prostanoid*</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Ambrisentan/sildenafil/prostanoid*</td>
<td>5 (13.9)</td>
</tr>
</tbody>
</table>

SD = standard deviation; PAH= Pulmonary Arterial Hypertension; IPAH= Idiopathic PAH; FPAH = Familial PAH; APAH = PAH associated with other diseases or risk factors; WHO = World Health Organization; 6MWD = 6-minute walk distance; BDI = Borg dyspnea index.

*Prostanoid therapies included epoprostenol and treprostinil. No subject was receiving inhaled iloprost.
Table 2—Maximum Liver Function Test Elevations Associated with Previous ERA Use

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bosentan</th>
<th>Sitaxsentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued ERA therapy, n*</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>ALT/AST &gt; 3xULN and ≤ 5xULN, n (%)</td>
<td>11 (32.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>ALT/AST &gt; 5xULN and ≤ 8xULN, n (%)</td>
<td>14 (41.2%)</td>
<td>4 (80.0%)</td>
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<tr>
<td>ALT/AST &gt; 8xULN, n (%)</td>
<td>9 (26.5%)</td>
<td>1 (20.0%)</td>
</tr>
<tr>
<td>Median duration of ERA therapy prior to discontinuation, weeks</td>
<td>13.9</td>
<td>28.7</td>
</tr>
</tbody>
</table>

ERA = endothelin receptor antagonist; ALT/AST = alanine aminotransferase and/or aspartate aminotransferase; ULN = upper limit of normal.
*3 patients discontinued both bosentan and sitaxsentan.
Study design
254x190mm (96 x 96 DPI)
Kaplan-Meier curve of the time to first event. Time to first event is defined as alanine aminotransferase or aspartate aminotransferase level $>3\times$ULN. Symbol (+) on the curve indicates the time at which subjects were censored.

*36 patients at risk at week 0

254x190mm (96 x 96 DPI)
Mean change from baseline in 6MWD (A), BDI (B), and WHO functional class (C). Error bars in 3A and 3B represent standard error of the mean.

254x190mm (96 x 96 DPI)
Ambrisentan Therapy in Patients with Pulmonary Arterial Hypertension Who Discontinued Bosentan or Sitaxsentan Due to Liver Function Test Abnormalities


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