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Clinical Safety, Pharmacokinetics, and Efficacy of Ambrisentan Therapy in Children With Pulmonary Arterial Hypertension

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Summary

Recent trials in adult PAH revealed the efficacy of ambrisentan. However, in children with PAH, the clinical safety and pharmacokinetics of ambrisentan has not been well studied. Our aim was to investigate the clinical safety, pharmacokinetics, tolerability, and efficacy of endothelin receptor antagonist therapy with ambrisentan in children with pulmonary arterial hypertension (PAH). This retrospective cohort study provides clinical data from pediatric patients with PAH receiving ambrisentan as add-on therapy or transition from bosentan. Safety included evaluation of adverse events including aminotransferase abnormalities. The clinical impact was evaluated by improvement from baseline in clinical variables. A total of 38 pediatric patients with PAH received ambrisentan. Fifteen of 38 patients were switched from bosentan to ambrisentan. The remaining 23 children were treated with ambrisentan as an add-on therapy due to disease progression. In both transition and add-on cases, mean pulmonary artery pressure significantly improved (transition; 55 ± 18 vs. 45 ± 20 mmHg, $n = 13$, $P = 0.04$, add-on; 52 ± 17 vs. 45 ± 19 mmHg, $n = 13$, $P = 0.03$) during the follow-up. World Health Organization functional class improved in 31% of patients, but one patient required an atrial septostomy due to disease progression during the follow-up period (median, range; 20, 4–44 months). Five patients (13%) discontinued ambrisentan due to severe headache, lack of clinical efficacy, or near syncope. Ten patients (26%) had side effects associated with ambrisentan treatment, including nasal congestion, headache, and flushing. However, no patients had aminotransferase abnormalities and there were no deaths after initiation of ambrisentan during follow-up. Pharmacokinetics were evaluated in sixteen children treated with ambrisentan from 2.5 mg to 10.0 mg; the mean peak plasma concentration was 738 ± 452 ng/ml, mean time to peak plasma concentration was 3.2 ± 2.1 hours, and mean area under the curve plasma concentration was 6657 ± 4246 ng·hour/ml. In conclusion, initial experience with ambrisentan in children suggests that treatment is safe with similar pharmacokinetics to those in adults and may improve PAH in some children.

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Keywords

endothelin receptor antagonists; safety; tolerability; World Health Organization

INTRODUCTION

Endothelin-1 (ET-1) was initially isolated from endothelial cell cultures in 1988 by Yanagisawa.¹ Since the discovery of ET-1, over-expression of ET-1 has been demonstrated in patients with pulmonary arterial hypertension (PAH).²⁻⁶ ET-1 is a potent vasoconstrictor and is mediated by two types of endothelin receptors including type A and type B. The Food and Drug Administration (FDA) has approved two endothelin receptor antagonists (ERA), bosentan and ambrisentan, in adults with PAH. Ambrisentan differs from bosentan as it is highly selective for the endothelin type A receptor whereas bosentan is a dual antagonist. Ambrisentan is indicated for once-daily treatment of PAH to improve exercise capacity and delay clinical worsening in adults with World Health Organization (WHO) functional class II or III symptoms.⁷⁻¹⁰ The two pivotal trials of ambrisentan in PAH were randomized, double-blind, placebo-controlled, multicenter, and efficacy studies (ARIES) in adults with idiopathic PAH or PAH associated with connective tissue disease, anorexigen use, or HIV infection.¹¹ The ARIES trials demonstrated the efficacy and safety of ambrisentan through improvements in exercise tolerance, WHO functional class, and Borg dyspnea score with good safety and tolerability. The safety concerns of endothelin receptor antagonists are mainly related to hepatotoxicity, decreasing hemoglobin level, and teratogenicity.⁷ In the treatment of PAH patients, ambrisentan is associated with a lower incidence of liver function test abnormalities compared to bosentan.¹¹⁻¹⁴

Recently, FDA removed the black box warning for liver function tests in the ambrisentan label. However, in children with PAH, the safety, pharmacokinetics and clinical efficacy of ambrisentan therapy have not been well studied. Our aim was to investigate the pharmacokinetics, clinical safety, tolerability, and efficacy of ambrisentan therapy in children with PAH after transition from bosentan and in those receiving ambrisentan as add-on therapy.

METHODS

Study Population and Outcome Measures

This retrospective cohort study was performed using clinical data from pediatric patients with PAH receiving commercially available ambrisentan. All patients were enrolled in an IRB approved protocol for patient follow-up and treated with ambrisentan from July 2007 to September 2011 at Children's Hospital Colorado, Denver and Columbia University Medical Center, New York. The clinical impact of ambrisentan was evaluated by WHO functional class, plasma brain natriuretic peptide, and catheterization at baseline and follow-up after administration of ambrisentan in a subset of patients.

By right heart catheterization using a flow directed Swan-Ganz catheter and a systemic arterial line for monitoring, we measured mean right atrial pressure, mean pulmonary artery pressure, mean systemic blood pressure, and pulmonary capillary wedge pressure. Accordingly, we calculated pulmonary vascular resistance index and pulmonary vascular resistance/systemic vascular resistance ratio. Cardiac output was obtained using thermodilution and cardiac index was calculated. If a significant intra-cardiac defect remained, cardiac output was obtained by the Fick method using the LaFarge estimation. Plasma brain natriuretic peptide (BNP) was assayed on an i-STAT® system using the two-site enzyme-

linked immunosorbant assay (Abbott Laboratories, IL). A cutoff of 100 pg/ml was chosen as the cutoff for BNP level as it is the upper normal value in our laboratory.

Side effects, laboratory evaluations, including monthly liver function tests, pregnancy tests in girls of child-bearing potential, and clinical worsening were used to assess safety and tolerability. Side effects such as headache, flushing, myalgia, peripheral edema, nasal congestion, and abnormalities of liver function tests were monitored at each clinic visit at 3 months intervals. Liver function tests including aspartate aminotransferase, alanine aminotransferase, and total bilirubin were assessed monthly. Aminotransferase abnormalities were defined as elevation of concentrations over 2× the upper limit of normal resulting in dose reduction or eventual discontinuation of ambrisentan. Clinical worsening which included the initiation of additional PAH medications, hospitalization due to deterioration of PAH symptoms, septostomy, and death due to heart failure were determined. Other clinical variables included evaluation for chest pain, syncope, nausea, dyspnea with exercise, and reason for discontinuation of ambrisentan. One patient was previously described in a manuscript of ambrisentan in Eisenmenger syndrome.⁸

The pharmacokinetic (PK) evaluation was an open-label, non-controlled, multiple-dose study in patients receiving ambrisentan for at least 30 days. Blood samples for ambrisentan PK assessments were collected at pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, and 12 h post-dose. We analyzed peak plasma concentration ($C_{\max}$) and time to $C_{\max}$ ($T_{\max}$) from the concentration data. In addition, we calculated the area under the plasma concentration–time curve during a dose interval (AUC) and the AUC from time 0 to infinity, AUC (0- ∞).

Statistical Methods

All analyses included patients with baseline and at least one post-baseline measure. At baseline and after start of treatment, clinical data was abstracted. In a patient on ambrisentan where treatment was terminated due to worsening of the disease, the clinical data were obtained and the last observation was used for analysis. The missing values for all measurements were excluded from the analysis. All results are reported as median and range or mean $\pm$ standard deviation along with the 95% confidence interval as appropriate. Comparisons of natriuretic peptide levels and hemodynamic variables between baseline and after initiation of ambrisentan were performed using Student *t*-tests, or Mann-Whitney's *U*-test as appropriate. For longitudinal data, analysis was performed with repeated measures. The level of statistical significance was defined as *P*-value of 0.05. Analyses were conducted using Statmate III for Windows (Atoms Co., Tokyo, Japan).

RESULTS

Demographic Data

A total of 38 pediatric patients with PAH received ambrisentan during the observational period. The median (range) and mean ($\pm$ standard deviation) age was 11 years old (2–18 years old) and 10.1 ± 4.1 years old with 50% being female. The etiologies of PAH included idiopathic PAH ($n = 19$), PAH associated with congenital heart disease ($n = 15$), PAH associated with connective tissue disease ($n = 1$), and others ($n = 3$; heritable, pulmonary capillaritis, and bronchopulmonary dysplasia). Among patients with congenital heart disease, six patients underwent cardiac surgery before initiation of ambrisentan therapy. The remaining nine patients with unrepaired congenital heart disease had atrial septal defect ($n = 2$), ventricular septal defect ($n = 2$), patent ductus arteriosus ($n = 2$), atrioventricular septal defect ($n = 1$), aortopulmonary window ($n = 1$), and isolated pulmonary artery of ductal origin ($n = 1$). Among these patients, eight patients were classified as Eisenmenger syndrome due to mild to moderate desaturation. The baseline concomitant vasodilator

therapies included infusion of treprostinil or epoprostenol, iloprost, sildenafil, and tadalafil. Thirty-three patients (87%) received a phosphodiesterase type 5 inhibitor and ambrisentan as combination therapy (Table 1).

Ambrisentan Dose

Eleven patients started 2.5 mg of ambrisentan as an initial dose while the remaining 27 patients started 5 mg. In patients who were greater than 40 kg, the initial ambrisentan dose was 5 mg and patients who were <20 kg received 2.5 mg of ambrisentan as the initial dose (Table 2). Of the 27 patients who received the 5 mg dose, 10 patients (37%) were up-titrated to 10 mg over several months. In contrast, all patients who received 2.5 mg were titrated upward to 5 mg. Overall, 20 patients had a dosage increase to 5 or 10 mg. Dose reduction due to adverse events, including aminotransferase concentrations abnormalities, was not required in any patient. Thus, the ambrisentan dose achieved was 5 or 10 mg/day (0.19 ± 0.1 mg/kg/day).

Transition Cases From Bosentan To Ambrisentan And Add-On Cases

Fifteen of 38 patients (40%) were switched from bosentan to ambrisentan. The remaining 23 children (60%) were treated with ambrisentan as an initial ERA therapy due to disease progression. In the transition cases, the reason for transition included once daily dosing ($n = 8$), elevation of liver enzyme on bosentan ($n = 3$), side effects ($n = 3$), and lack of efficacy ($n = 1$). The dose of bosentan was from 15.125 to 125 mg twice a day (3.0 ± 1.4 mg/kg/day) and initial dose of ambrisentan was 2.5 or 5 mg (0.15 ± 0.1 mg/kg/day). Twelve of 15 transition patients (80%) were on background phosphodiesterase type 5 inhibitor.

Plasma Brain Natriuretic Peptide

There were no significant differences in BNP before and after initiation of ambrisentan (Table 3). In 12 transition cases, BNP was normalized in one patient after transition, but BNP was increased in three patients. In 16 add-on cases, BNP was normalized in two patients, but BNP was increased in one patient after initiation of ambrisentan. Therefore, 3 of 28 patients had abnormal BNP levels before initiation of ambrisentan and 4 of 28 patients had abnormal BNP levels after initiation of ambrisentan. Twenty-one of 38 patients had normal BNP levels before and after ambrisentan treatment.

Hemodynamics

In transition cases, ambrisentan significantly improved mean pulmonary artery pressure (55 ± 18 vs. 45 ± 20 mmHg, $n = 10$, $P = 0.04$) compared with bosentan therapy during follow-up (median, range; 21, 12–42 months) (Table 3). Likewise, add-on cases demonstrated a reduction in mean pulmonary artery pressure (52 ± 17 vs. 45 ± 19 mmHg, $n = 13$, $P = 0.03$) during follow-up (median, range; 23, 10–60 months). Add-on cases include three patients who have residual shunt including patent ductus arteriosus or aortopulmonary window. When we excluded these three patients from add-on cases, we still found a significant difference in mean pulmonary artery pressure (48 ± 16 vs. 35 ± 10 mmHg, $P = 0.03$) during follow-up (median, range; 23, 12–60 months) in 10 add-on cases.

Figure 1 shows the longitudinal change in mean pulmonary artery pressure before and after initiation of ambrisentan therapy. Other hemodynamic parameters, such as cardiac index, pulmonary vascular resistance index, and pulmonary vascular resistance/systemic vascular resistance ratio did not change.

When we evaluated patients with idiopathic PAH or repaired congenital heart disease, the four patients with repaired congenital heart disease did not have an improvement in mean pulmonary artery pressure (41 ± 15 vs. 34 ± 17 mmHg) after initiation of ambrisentan,

whereas there was significant improvement in mean pulmonary artery pressure (54 ± 17 vs. 41 ± 16 mmHg, $P = 0.005$) in the 16 patients with idiopathic PAH. Cardiac index (4.5 ± 1.3 vs. 4.3 ± 1.2 L/min/m²), pulmonary vascular resistance index (10.8 ± 5.3 vs. 9.4 ± 5.3 unitxm²), and pulmonary vascular resistance/systemic vascular resistance ratio (0.78 ± 0.36 vs. 0.62 ± 0.34) were unchanged in patients with idiopathic PAH.

WHO Functional Class

Three patients did not have evaluation of WHO functional class after initiation of ambrisentan due to discontinuation. In add-on cases, at baseline, 80% of the patients were in WHO functional class II with the remainder being class III or IV (15% and 5%, respectively). During follow-up, none of patients with class III and IV improved functional class, but 6 patients (30%) with class II improved to class I. In transition cases from bosentan therapy, 40% of patients were class I, 33% were class II, 20% were class III, and 7% were class IV. After transition to ambrisentan, the patients with class IV did not change functional class, but all patients with class III improved to class II, and 2 patients improved from class II to class I. Overall, WHO functional class improved in 11 of 35 patients (31%) during follow-up (median, range; 20, 4–44 months) (Fig. 2).

Safety

Most adverse events were mild to moderate. Side effects of ambrisentan were observed in 10 patients (26%, two patients, 10 mg; eight patients, 5 mg). The mean body weight adjusted dose of ambrisentan in 10 patients with side effects was 0.17 ± 0.06 mg/kg/day compared to 0.19 ± 0.09 mg/kg/day in patients without side effects, suggesting no dose related side effects. The side effects included nasal congestion ($n = 9$, 24%), headache ($n = 3$, 8%), and flushing ($n = 1$, 3%) (Table 4). Five patients discontinued ambrisentan, thus the discontinuation rate was 13% in all patients on ambrisentan therapy. Two patients discontinued due to headache as a side effect and two patients stopped ambrisentan due to lack of clinical efficacy. One patient discontinued due to near syncope after transition from bosentan therapy and switched back to bosentan therapy. There was no elevation of liver function tests including aspartate aminotransferase, alanine aminotransferase, and total bilirubin after initiation of ambrisentan during follow-up.

Clinical Worsening

PAH symptoms on ambrisentan therapy were similar compared with those before initiation (Table 5a). The incidence of side effects and PAH symptoms after initiation of ambrisentan were not different between patients with congenital heart disease and those with idiopathic PAH. Of all, only three patients required additional PAH therapy and one patient underwent septostomy due to deterioration after initiation of ambrisentan (Table 5b). However, no patients died after initiation of ambrisentan during follow-up.

Pharmacokinetics

Sixteen children aged 3 to 15 years with a body mass index of 13.4–22.4, weight of 13–72.7 kg, with IPAH or secondary PAH including congenital heart disease, chronic lung disease, and pulmonary capillaritis were enrolled in the PK study. Characteristic data in 16 patients are shown in Table 6. Of all, 2 patients received 2.5 mg and 3 patients received 10.0 mg of ambrisentan at once daily dose. In the remaining 11 patients, 5.0 mg of ambrisentan was taken. The PK data in 16 patients on ambrisentan therapy is shown in Table 7.

DISCUSSION

This retrospective observational cohort study demonstrates clinical safety and potential efficacy of ambrisentan therapy in pediatric patients with PAH. We found that once-daily administration of ambrisentan therapy improved WHO functional class in 31% of patients and pulmonary arterial pressure in the subset of pediatric PAH patients who underwent heart catheterization, with no elevation of aminotransferase levels. Furthermore, ambrisentan therapy allowed 14 of 15 patients to be successfully switched from bosentan to ambrisentan. Our study is interesting because this is the first report to evaluate clinical variables, including hemodynamics, in children with PAH treated with ambrisentan.

In the previous controlled clinical trials (ARIES), there were no reports of elevated aminotransferase levels in the ambrisentan groups.¹¹ Peripheral edema, headache, and nasal congestion were the most common adverse events with ambrisentan. The adverse events in this study were similar to adult studies, except that peripheral edema was rare in children. The most frequently reported side effect was nasal congestion in our study population. Side effects were observed in 10 patients who received similar body weight adjusted doses of ambrisentan compared with in the other patients. Therefore, our results demonstrate that no apparent dose response was noted for adverse events due to ambrisentan in pediatric patients. In addition, the safety profile and incidence of clinical worsening were similar to those observed in other randomized clinical trials.^{11,14}

Each patient received 2.5 or 5 mg of ambrisentan once-daily and increased dosage to 5 or 10 mg once-daily with absence of severe side effects and adequate tolerability in our patients. In the clinical setting, pediatric patients can be started on ambrisentan at the initial 2.5 (<20 kg) or 5 mg dose (>20 kg) and considered for an up-titration to the 5–10 mg dose. However, there was no predefined protocol in our study.

An explanation for the improvement of clinical variables, such as hemodynamics, in transition cases is unclear. One possible reason could be explained by the potential drug interaction in patients who administered bosentan and phosphodiesterase type 5 inhibitors. In our transition cases, 80% of patients were on background phosphodiesterase type 5 inhibitor such as sildenafil together with bosentan or ambrisentan. Bosentan causes a decrease in exposure of co-administered drugs metabolized by the cytochrome P450 pathway including sildenafil,¹⁵ and tadalafil.¹⁶ In contrast, ambrisentan has no drug interaction with sildenafil or tadalafil which are commonly used in pediatric patients with PAH.¹⁷ Therefore, the absence of a drug–drug interaction might have been a reason for the improvement in hemodynamics. In addition, sedation or decrease in cardiac index may have contributed to the fall in mean pulmonary artery pressure at catheterization.

The hepatic safety profile was favorable, with no elevation in aspartate aminotransferase or alanine aminotransferase concentrations requiring drug discontinuation. Bosentan is primarily eliminated by hepatic metabolism through the P450 enzyme systems CYP2C9 and CYP3A4.^{18,19} In contrast to bosentan, ambrisentan is primarily metabolized via hepatic glucuronidation^{14,20} and is not strongly influenced by CYP pathways. There were no aminotransferase abnormalities in patients taking ambrisentan in the placebo controlled clinical trials.¹¹ These data suggested ambrisentan may have a clinical advantage regarding effects on hepatobiliary biology. We continue regular monitoring of aminotransferase level every 3 months in children due to concern for a class effect of ERAs, despite the change in the FDA drug label.

There is no known ambrisentan dose for pediatric populations and the doses administered in this study were extrapolated from the adult dose range. In the present study, doses of 5 or 10 mg might be considered as therapeutic in children, as the C_{max} and AUC in children were

similar to those in adults after exposure to 5 to 10 mg dose which showed clinical improvement.^{14,20,21}

Limitations of this study included the small sample size, open-label design, the lack of a placebo group, relative heterogeneity of the patients, and a relatively short observational duration. A larger, controlled study will be needed to determine whether the safety results observed in pediatric patients with PAH are seen in a larger population. Although the sample size was small, our pediatric patients did show improvement in hemodynamics and WHO functional class in some patients. Although the pharmacokinetics in our study seemed similar to adults, further pharmacokinetic evaluation is necessary. We tended to increase ambrisentan from 5 to 10 mg in patients > 20 kg with more severe PAH, but no protocol was followed, and further studies are required to determine the optimal dose.

The patients in this study are representative of the patients seen in a typical pediatric pulmonary hypertension clinic. Although this study has several limitations, we found that ambrisentan may have a favorable safety profile and potential efficacy in some pediatric patients with PAH.

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Fig. 1.

Mean pulmonary artery pressure at catheterization before and after initiation of ambrisentan therapy. The figure displays the longitudinal change in mean pulmonary artery pressure before and after initiation of ambrisentan therapy. The time of onset of ambrisentan therapy is zero with the number of months before and after ambrisentan therapy on *x*-axis. a: Transition cases (*n* = 10). In 7 of 10 patients with cardiac catheterization data before and after ambrisentan therapy, mean pulmonary artery pressure was improved after transition from bosentan therapy. b: Add-on cases (*n* = 13). In 11 of 13 patients with cardiac catheterization data before and after ambrisentan therapy, mean pulmonary artery pressure was improved after add-on ambrisentan therapy.

Fig. 2. Change in WHO Functional Class between baseline and initiation of ambrisentan therapy. In transition and add-on cases, WHO functional class II or III patients improved to class I or II. WHO; World Health Organization.

TABLE 1
Clinical Characteristics at Baseline

	All	Transition (on bosentan)	Add-on
Total number	38	15	23
Age (year-old)			
Median (range)	11 (2–18)	9 (6–17)	11 (2–18)
Mean $\pm$ standard deviation	10.1 $\pm$ 4.1	10.3 $\pm$ 3.6	10.0 $\pm$ 4.5
Gender (male/female)	19/19	8/7	11/12
Pathogenesis (number)			
Idiopathic	19	10	9
Congenital heart disease	15	3	12
Connective tissue disease	1	1	0
Others	3	0	3
Race (number)			
White	28	8	20
Hispanic	5	4	1
Black	5	3	2
Concomitant therapy (number)			
Treprostinil ^I	17	5	12
Epoprostenol	6	3	3
Iloprost	3	2	1
Sildenafil	28	11	17
Tadalafil	5	1	4
WHO functional class (number)			
Class I	6	6	0
Class II	21	5	16
Class III	6	3	3
Class IV	2	1	1

^I Intravenous, subcutaneous, or inhaled.

TABLE 2

Ambrisentan Dose in Different Body Weight

Patient body weight (kg)	Initial dose (patients number)	Current dose (patients number)	Discontinue patients (patients number)
<20	2.5 mg (3)	5 mg (3)	(0)
20–40	2.5 mg (8), 5 mg (12)	5 mg (13), 10 mg (4)	2.5 mg (1), 5 mg (2)
>40	5 mg (15)	5 mg (7), 10 mg (6)	5 mg (2)

TABLE 3
Clinical Variable Changes After Initiation of Ambrisentan Therapy in Transition Cases and Add-On Cases

Clinical variables	N	Transition		P-value	N	Add-on		P-value
		On bosentan	On ambrisentan			Before	After	
Brain natriuretic peptide (pg/ml)	12	49 ± 34	72 ± 47	NS	16	81 ± 105	53 ± 41	NS
Mean right atrial pressure (mmHg)	10	74	73	NS	10	63	72	NS
Mean pulmonary artery pressure (mmHg)	10	55 ± 18	45 ± 20	0.04	13	52 ± 17	45 ± 19	0.03
Pulmonary vascular resistance index (unit × m ²)	10	10.1 ± 5.6	9.3 ± 5.9	NS	13	11.3 ± 6.0	10.6 ± 8.7	NS
Pulmonary/systemic vascular index ratio	10	0.8 ± 0.3	0.6 ± 0.4	NS	13	0.9 ± 0.8	0.8 ± 0.9	NS
Cardiac index (L/min/m ²)	10	4.8 ± 1.4	4.0 ± 1.2	NS	13	4.5 ± 1.2	4.5 ± 1.5	NS

N: number, NS: not significant.

TABLE 4
Side Effects on Ambrisentan Therapy

Side effects	All patients (%), N = 38	Transition (%), N = 15	Add-on (%), N = 23
Nasal congestion	9 (24)	3 (20)	6 (26)
Headache	3 (8)	1 (7)	2 (9)
Myalgia	0 (0)	0 (0)	0 (0)
Flushing	1 (3)	0 (0)	1 (4)
Edema	0 (0)	0 (0)	0 (0)
Liver dysfunction	0 (0)	0 (0)	0 (0)

TABLE 5a
Clinical Symptoms and Worsening After Initiation of Ambrisentan Therapy

	Before number (%)	After number (%)
Symptoms due to PAH ^I		
Chest pain	2 (5)	2 (5)
Dizziness	1 (3)	1 (3)
Syncope	1 (3)	1 (3)
Fatigue	8 (21)	8 (21)
Nausea	1 (3)	1 (3)
Dyspnea	17 (45)	14 (37)
Hemoptysis	1 (3)	1 (3)

Clinical symptoms before and after initiation of ambrisentan therapy in all patients (n = 38).

^IPAH, pulmonary arterial hypertension.

TABLE 5b
Clinical Symptoms and Worsening After Initiation of Ambrisentan Therapy

Clinical worsening	All patients (%), N = 38	Transition (%), N = 15	Add-on (%), N = 23
Hospitalization due to heart failure	3 (8)	1 (7)	2 (9)
Septostomy	1 (3)	1 (7)	0 (0)
Initiation of other PAH drugs [/]	3 (8)	0 (0)	3 (13)
Death	0 (0)	0 (0)	0 (0)

Incidence of clinical worsening on ambrisentan therapy.

[/] All patients had inhalation of treprostinil.

TABLE 6
Demographics in Patients Administered Ambrisentan for Pharmacokinetic Study

Subjects	Dose (mg)	Age (year-old)	Diagnosis	BSA (m ²)	BMI (Kg/m ²)	Side effect	Clinical worsening
1	2.5	3	PAH associated CHD	0.60	14.6	—	—
2	2.5	5	IPAH	0.75	17.6	Nasal congestion	New drug ¹
3	5.0	4	PAH associated CLD	0.59	13.8	Nasal congestion	—
4	5.0	5	IPAH	0.73	14.7	—	—
5	5.0	8	IPAH	1.02	18.6	—	—
6	5.0	8	IPAH	0.88	13.4	Nasal congestion	—
7	5.0	8	PAH associated pulmonary capillaritis	1.07	16.6	—	Hospitalized
8	5.0	9	PAH associated CHD	0.87	13.5	—	—
9	5.0	11	IPAH	1.49	22.0	—	—
10	5.0	12	PAH associated CHD	1.20	19.5	Nasal congestion	—
11	5.0	13	IPAH	1.36	16.9	—	—
12	5.0	14	IPAH	1.15	15.3	—	—
13	5.0	15	IPAH	1.91	22.4	—	—
14	10.0	9	IPAH	1.14	17.0	—	—
15	10.0	10	IPAH	1.08	15.4	—	—
16	10.0	15	PAH associated CHD	1.37	15.5	—	—
Mean ± SD	—	9.3 ± 3.8	—	1.08 ± 0.35	16.7 ± 2.8	—	—

BSA, body surface area; BMI, body mass index; CHD, congenital heart disease; CLD, chronic lung disease; IPAH, idiopathic pulmonary arterial hypertension; SD, standard deviation.

¹New drug: initiation of additional PAH drug.

TABLE 7
Pharmacokinetic Parameters of Ambrisentan at 2.5, 5, or 10 mg

Subject	Dose (mg)	Body weight (Kg)	Dose Adjusted for body weight (mg/kg)	C _{max} (ng/mL)	Dose Adjusted C _{max} (ng/mL/mg)	T _{max} (hr)	AUC _{0-tau} (ng · hr/mL)	Dose Adjusted AUC _{0-tau} (ng · hr/mL/mg)	T _{1/2} (hr)
1	2.5	13.5	0.19	984	394	4.0	7710	3080	5.4
2	2.5	19.4	0.13	525	210	2.0	3730	1490	8.2
3	5.0	13.0	0.38	480	96.0	1.0	2450	490	6.1
4	5.0	17.5	0.29	990	198	3.0	7980	1600	7.1
5	5.0	29.6	0.17	550	110	4.0	4980	996	6.0
6	5.0	22.0	0.23	907	181	4.0	8590	1720	7.0
8	5.0	21.4	0.23	635	127	2.0	6250	1250	6.3
9	5.0	52.1	0.10	556	111	3.0	6660	1330	15.3
10	5.0	37.4	0.13	457	91	2.0	3320	664	5.7
11	5.0	42.2	0.12	571	114	3.0	5000	1000	7.4
12	5.0	32.6	0.15	900	180	1.0	4408	882	8.0
13	5.0	72.7	0.07	289	58	2.0	3410	682	9.6
14	10.0	33.3	0.30	571	57	8.0	7850	785	NC
15	10.0	30.2	0.33	2230	223	2.0	20900	2090	NC
16	10.0	41.3	0.24	386	38.6	8.0	7250	725	NC
Mean ± SD	—	31.8 ± 15.4	0.20 ± 0.09	738 ± 452	147 ± 87	3.2 ± 2.1	6657 ± 4246	1249 ± 656	7.6 ± 2.6

NC, not calculated; AUC, area under the plasma concentration–time curve during a dose interval; C_{max}, peak plasma concentration; T_{max}, time to C_{max}; T_{1/2}, half life.