

Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children

Alison A Hislop<sup>1,2\*</sup>, Shahin Moledina<sup>1\*</sup>, Harriet Foster<sup>1</sup>, Ingram Schulze-Neick<sup>1</sup>, Sheila G Haworth<sup>1,2</sup>

1. Great Ormond Street Hospital for Children and 2. Institute of Child Health, University College London, London, WC1N 1EH, UK

\* joint first authors

Address for correspondence:

Dr Alison A Hislop  
UCL Institute of Child Health  
30 Guilford Street  
London WC1N 1EH  
Tel: 020-7905-2337  
Fax: 020-7905-2321  
Secretary 020-7242 9200 ext 1005  
e-mail: a.hislop@ich.ucl.ac.uk

## **Abstract**

To evaluate a 5 year experience using bosentan in children with pulmonary arterial hypertension (PAH) a retrospective, observational study was made of children in the UK Pulmonary Hypertension Service for Children given bosentan as monotherapy or in combination from February 2002 until May 2008 and followed up for at least 6 months.

Detailed studies were made of 101 children with idiopathic PAH (42) and PAH associated with congenital heart disease (59). Before treatment, WHO Functional Class, 6-minute walk distance (6MWD), height, weight and haemodynamic data were determined. Evaluations were analysed after 6 months and annually to a maximum of 5 years. Median duration of treatment was 31.5 months. Initial improvement in WHO and 6MWD was maintained for up to 3 years. Height and weight increased but the z-scores did not improve. After 3 years, bosentan was continued as monotherapy in only 21% of children with IPAH, but in 69% of repaired cases and 56% of those with Eisenmenger Syndrome. The Kaplan-Meier survival estimates for the 101 patients were 96%, 89%, 83% and 60% at 1, 2, 3 and 5 years. A treatment regime which includes bosentan is safe and appears effective in slowing disease progression in children with PAH.

## **Key words**

bosentan in pulmonary hypertension, IPAH, Paediatric pulmonary arterial hypertension, pulmonary hypertension in congenital heart disease.

## **Introduction**

Endothelin-1 (ET) is important in the pathobiology of pulmonary arterial hypertension (PAH) [1-3] and plasma levels are elevated in both adults and children. Its actions are mediated principally by two receptors, ETA and ETB. The dual endothelin receptor antagonist bosentan, has been shown to be safe and efficacious in the treatment of adults with PAH [4,5]. Recent studies have shown that benefit is generally sustained for at least 1 year [6-9]. In children evidence for efficacy is limited. In 2003 a small 12-week trial of 19 children [10] showed that the drug was efficacious and could be used safely in the young. Two years later Rosenzweig et al [11] reported on 86 children with idiopathic PAH and PAH associated with either congenital heart disease or connective tissue disease. The median duration of exposure to bosentan was 14 months and the drug was considered efficacious, whether given as monotherapy or with a prostanoid. In 2006 we reported on 40 children treated for a mean of 12.7 months by the UK Pulmonary Hypertension Service. In those with idiopathic PAH (IPAH) clinical stability was maintained or achieved but 60% of the children also required epoprostenol [12]. Those with associated PAH showed a significant improvement in 6 minute walk distance (6MWD) and WHO functional class, the majority on monotherapy. In the present paper we describe a 5 year experience of using bosentan both as a monotherapy and in combination with a prostanoid and or the phosphodiesterase inhibitor sildenafil in 101 children with IPAH and pulmonary

hypertension associated with congenital heart disease treated with bosentan during this period .

### **Patients and Methods**

Between February 2002 and May 2008 101 children with IPAH (n=42, 2 cases familial) or PAH associated with congenital heart disease (APAH), either post-repair (n=31) or with the Eisenmenger Syndrome (n=28) were treated with bosentan.. Thirty-two of these patients, 20 IPAH and 12 APAH, have been the subject of our previous report on the short term efficacy of bosentan [12]. Twenty children had Trisomy 21, the majority of these having the Eisenmenger Syndrome (Table 1).

In all patients the investigations confirmed the presence of pulmonary arterial hypertension and determined its causality. An electrocardiogram, transthoracic echocardiogram, chest radiograph and where indicated computed chest tomography was carried out at presentation. Cardiac catheterisation was carried out under general anaesthesia. The pulmonary blood flow was calculated based on measured oxygen consumption in the majority of cases and acute vasodilator testing was carried out using inhaled nitric oxide (NO). Baseline haemodynamic data were recorded (Table 1).

The treatment algorithm used was based on the European Society of Cardiology algorithm for the management of adult patients with IPAH and the national guidelines [13, 14] adapted for children. The few children with a positive response to acute vasodilator testing with nitric oxide at cardiac catheterisation were given a calcium channel antagonist, nifedipine. For the non-responders, in IPAH and post-operative pulmonary hypertension all functional class IV patients were treated with epoprostenol at presentation, as were the severely symptomatic children in functional class III.

Less symptomatic children in class III were treated with bosentan either as monotherapy or in combination with sildenafil with escalation of therapy if they failed to demonstrate a response. Children with unrepaired congenital heart disease received bosentan or bosentan was added to the sildenafil they were receiving before referral to the Service. Those with IPAH and post-operative pulmonary hypertension were anticoagulated with warfarin but the small children were given aspirin. The therapeutic regimen was tailored to the needs of each child and adjusted according to response. The target dose of bosentan was 31.5-125mg twice a day according to weight [11,12]. Children less than 10 Kg were given 15 mg twice daily. If patients deteriorated on bosentan monotherapy, then sildenafil or epoprostenol were added as required. All children were known to have normal liver function and haematological studies before bosentan was prescribed.

It should be noted that management changed as new drugs became available during the course of the study period, from early 2002.

Of the 101 cases with IPAH and congenital heart disease bosentan was given to 67 as monotherapy (24 with IPAH and 43 APAH). Fifty-eight of these children had not been treated previously (treatment naïve) and nine had their medication changed to bosentan. In 34 patients (18 IPAH and 16 APAH) bosentan was added to an existing pulmonary hypertension specific therapy, either sildenafil or a prostanoid or both. Immediately before starting treatment, the weight, height and WHO functional class were determined. The 6MWD was measured in those children old enough and developmentally able to carry out the test successfully (n=51). In fifty-nine of the 101 children (24 IPAH, 16 repaired defects, 19 Eisenmenger Syndrome) the height, weight, WHO and 6MWD, had also been recorded approximately 6 months (4.9 SD2.8) before

being started on bosentan, and 23 (39%) of these children were already on alternative specific treatment for pulmonary hypertension.

In all children, the weight, height and WHO functional class and 6MWD were assessed at 6 months (6.3m SD 1.4), 1 year (12.2m SD 1.5), 2 years (23.9m SD 2.02), 3 years (35.5m SD 1.8), 4 years (47.9m SD 1.7) and 5 years (60.3m SD 1.8) after starting treatment with bosentan. Liver function tests were carried out at monthly intervals. Nineteen children had a second cardiac catheterisation study. Initiation of additional therapies and discontinuation of bosentan was noted.

### **Statistical Methods**

Data are presented as mean and standard deviation (SD) or median and interquartile range as appropriate. Height and weight are expressed as standard deviation scores (z-scores) based on data from normal British children[15] or data specific for children with Down's syndrome[16]. The distance walked in six minutes is expressed as a percentage of predicted based on a published regression equation for children [17].

The Kruskal-Wallis test was used to compare variables between diagnostic groups. Comparison of height z-score, weight z-score, six minute walk distance between baseline and follow-up visits was performed using the paired t-test. The Wilcoxon matched paired test was used to test the significance of changes in WHO functional class over the appropriate time intervals. Survival, assessed from starting bosentan to death/ end of study date, was summarised using Kaplan-Meier estimates. Patients were censored at transplantation, discontinuation of bosentan or the end of follow-up. Treatment failure in the monotherapy group was defined as time from starting bosentan to discontinuation of bosentan for any reason, initiation of additional medical therapy, transplantation or death. Statistical analysis was performed using GraphPad Prism version 4.0 (GraphPad Software Inc, San Diego, CA, USA). This work was

approved by the ethics committee of Great Ormond Street Hospital and UCL Institute of Child Health.

## **Results**

### **Baseline characteristics**

Findings at the start of bosentan treatment (baseline) are shown in Table 1. The mean age at the start of treatment was 9.7years (SD 5.5). The youngest child treated was one month old. Females predominated, the sex ratio being 1.63:1 in IPAH and 1.35:1 in APAH

Both height and weight were below normal (Table1) (Figure 1). The children with repaired CHD were of particularly low weight. The mean baseline WHO functional class was 2.8 (Figure 2) and both the mean and class distribution was similar in the different subgroups (Table1). Fifty-one children were able to perform a 6MWT reliably. Their mean age was 11.7 years. The mean distance walked was 258 metres (SD 127), 40.7% of the predicted for age (Figure 3a and b). There was no significant difference between the different diagnostic groups. Comparing children with and without Down syndrome, there was no difference at baseline in the percent of predicted 6-minute walk distance and WHO functional class.

Seventy-nine children had a cardiac catheterisation study (Table 1). The pulmonary artery pressure and pulmonary vascular resistance was significantly higher in those with IPAH and the Eisenmenger Syndrome than in the repaired CHD cases.

### **Clinical change prior to initiation of bosentan therapy**

The 59 children (mean age 10.3 years, SD 5.4) assessed approximately 6 months (mean 4.9 months) prior to starting bosentan therapy had deteriorated during this time interval. They had failed to thrive. The z-score for height deteriorated from -0.81(1.65) to -1.08(1.4) ( $p=0.08$ ) and the score for weight fell from -0.76 (1.6) to -0.93 (1.7) ( $p=0.02$ ) (Figure 1). The mean WHO score had deteriorated from 2.5 to 2.8 by the time bosentan therapy was started ( $p=0.04$ ) (Figure 2). The 6MWD was recorded before treatment in 15 of these children and at 39% of the predicted value had not changed significantly by the time bosentan was first given (Figure 3).

### **Clinical Response to therapy**

The median duration of bosentan treatment was 31.5 months (range 6-73 months). There were no serious side effects. The liver function tests became abnormal in 3 children, necessitating dose reduction in one, temporary suspension of treatment for one month in one and replacement by sildenafil in the third child.

The height and weight z-scores did not change significantly during follow-up indicating no further deterioration in failure to thrive but no significant catch up growth (Figure 1). WHO functional class improved after 6 months' treatment, decreasing from a mean of 2.8 to 2.4 (SD 0.8)  $p<0.001$ . In the survivors, improvement was maintained for up to 3 years ( $n=48$ ) (Figure 2). All three subgroups showed an improvement in functional class and a similar pattern of response was seen whether bosentan was given as a monotherapy or as an add-on combined therapy.

Exercise tolerance also improved. The 6MWD increased from a baseline of 40.9% predicted (258 m,  $n=51$ ) to 49.3% predicted (312m) at 6 months ( $p<0.01$ ), an increase maintained at 1, 2 and 3 years ( $p<0.01$  for all years;  $n=51$ ,  $n=48$ ,  $n=39$  respectively)



(Figure 3a). The percentage of predicted distance walked increased from 42.9% to 58.6% ( $p<0.01$ ) at six months in those with IPAH while the repaired cases showed a significant increase to 57% but only after 1 year ( $p<0.01$ ) (Figure 3b). Although there was no significant difference between the 3 subgroups at the start of bosentan treatment, those with the Eisenmenger syndrome improved less than those in the other 2 groups combined at 6 months and 1 year ( $p<0.05$ ).

In the entire cohort there was no significant difference between those with or without Down syndrome in the response to treatment, nor specifically within the group of children with the Eisenmenger syndrome which had the majority of patients with Down syndrome.

On repeat cardiac catheterisation ( $n=19$ ) after a median of 17 months (range 8-33) there was no significant change in either mean PAP (48.8 (16.6) v. 48.3 (16.2) mmHg or PVRI (16.5 (2.6) v. 14.1 (2.0) units.m<sup>2</sup>). Fifteen of these patients were on bosentan as a monotherapy and catheterisation was carried out to confirm that they remained stable and needed no intensification of therapy. They were indeed found to be stable.

In the subgroup of 59 children who had been assessed approximately 5 months prior to treatment with bosentan, after 6 months of treatment there was a small but non-significant increase in z-score for height and weight, an increase in walk distance and decrease in WHO functional class. Their response to bosentan was not as great as that of the group as a whole (Figure 4). However, the survival of these 59 prior patients was not significantly different to the other cases, 94.8 %, 90.8%, 85.9% and 60.2% at 1, 2, 3 and 5 years versus 97.6%, 86.8%, 79.6%, 74.3%. ( $P=0.83$ )

### **Changes in Treatment**

Bosentan was discontinued in 7 children. One child had a persistently raised alanine transaminase (ALT) level to more than three times the upper limit of normal, even when the bosentan dose was decreased, but became normal when the drug was discontinued. One child with the Eisenmenger syndrome had mild systemic hypotension, one was successfully weaned off the drug and 4 repeatedly refused to have liver function tests carried out.

Escalation of therapy Of the 24 children with IPAH started on monotherapy, 14 (58%) required additional therapy for worsening of symptoms (Figure 5a). Sildenafil was added in 7, intravenous epoprostenol in 6, and both drugs in one child. Of the 43 with APAH who were started on monotherapy, 16 (37%) needed an additional medication (Figure 5a). Sildenafil was added in 12, epoprostenol in 2 and both drugs in 2 cases.

In those children in whom bosentan was added to an existing medication no further changes in treatment were made. Seven children, all with IPAH and on combination therapy, had a bilateral lung or heart lung transplant having been on bosentan for a mean time of 18.4 months. All are still alive a mean of 37 months later. Thus over the course of follow up bosentan was discontinued in seven patients, additional therapy was given to 30, seven patients underwent transplantation and 21 patients died. Those in whom bosentan was discontinued were still alive at the end of the study period.

### **Survival**

For the 101 patients the Kaplan-Meier survival estimates were 95%, 89% , 83% and 60% at 1, 2,3 and 5 years respectively. Eight children with IPAH and 13 children with

APAH died. The survival values for IPAH were 95%, 95% and 95% and 55% , for the repaired cases were 97%, 86%, 78% and 58%, and for the Eisenmenger Syndrome 92%, 84%, 74% and 74% at 1,2, 3 and 5 years respectively (Figure 5b) with no significant difference between the groups. The data for transplant free survival at 1, 2, 3 and 5 years in the IPAH group was 94, 83, 75 & 56 %.

## **Discussion**

The present paper shows that a treatment regime which includes bosentan is safe and efficacious in the long management of children with PAH. We have extended the findings of earlier studies [11,12] by showing that bosentan is efficacious for a median time of 31.5 months in a large cohort of children with pulmonary arterial hypertension. We previously reported on 40 children, those with IPAH showing stabilisation after a mean follow up of 12.7 months on bosentan while those with APAH showed a significant improvement in NYHA functional class, 6-minute walk distance and weight [12] . In the current series of 101 children with IPAH and APAH as a result of congenital heart disease improvement was seen within 6 months and could be maintained for up to 3 years, giving bosentan either as monotherapy or in combination with other specific therapies. Ten children were successfully maintained on bosentan for 5 years, half receiving the drug as a monotherapy. The drug appeared safe in that the AST levels became persistently elevated in only one child, confirming earlier paediatric studies [11, 12]. Recent postmarketing surveillance reported elevated transaminases in 2.7% of children compared with 7.8% in patients older than 12 years of age [18]. Young age should not be a deterrent to treatment with bosentan. The youngest child treated in the present study was one month old. Our experience

confirms that of others [19]. Also, a new paediatric formulation has just been trialled successfully and the formulation approved, easing the management of infants and young children[20]

Bosentan is used most widely in both children and adults with IPAH and congenital heart disease, and we focussed on these diagnostic groups in the present paper. The median follow up for these 101 children was 31.5 months, comparing favourably with the mean follow up of 24 months in an adult cohort with IPAH [8] and a median of 29 months in adults with the Eisenmenger Syndrome [9]. In the present study the 1 and 2 year survival for IPAH and for pulmonary hypertension associated with congenital heart disease combined was 95% and 89% respectively, with no significant difference in survival between the diagnostic groups nor between the Down syndrome and normal children. These figures compare favourably with the only other comparable paediatric study which showed a 2 year survival of 91% [11]. In adults with IPAH the survival of patients treated with bosentan as a first line therapy with the addition of other medicines as indicated was reported as 92% and 89% at 1 and 2 years in a European study [8] and 96% and 89% respectively in an American study [21]. In a recent detailed study of IPAH in children we found no difference in survival between incident and prevalent cases [22]

We had data on 59 children who had been assessed approximately 5 months before treatment with bosentan was started. In the interim these children deteriorated rapidly as judged by their height, weight, and WHO Functional Class. The need for prompt referral to a pulmonary hypertension specialist centre is self evident even when the symptomatology is mild. Early treatment has been shown to be beneficial in

adults[23]. In our 59 paediatric cases bosentan restored the clinical status to what it had been when the children first presented almost 5 months earlier., whether given as a monotherapy or added to an existing therapy. However, they did not catch up. Their values for weight, WHO and 6MWD during follow up were all less than in children treated more promptly, although each parameter was not significantly poorer.. Nor were the survival figures significantly different ( $p=0.83$ ). This mirrors the findings of the open label extension of the Breathe- 5 study on adults with the Eisenmenger Syndrome those who had previously been in the placebo arm did not increase their 6-minute walk distance after 24 weeks medication with bosentan as much as those patients treated with bosentan from the outset [24]. Assessing the efficacy of medicines is difficult in pulmonary hypertension, particularly in children. A positive effect is conventionally accepted as an improvement in exercise capacity, generally the 6MWD in adults and older children, WHO Functional Class, absence of need to give additional therapies or to transplant and improved survival. We found that both WHO Functional Class and the 6MWD improved within 6 months of starting treatment and improvement was maintained for at least 3 years, longer than previously reported. In adults with IPAH an improvement in 6MWD was seen at 4 months and maintained at one year [8] while improvement was seen for up to 2 years in those with the Eisenmenger Syndrome and other types of congenital heart disease [9]. A small study reported that an improvement in 6MWD seen after four months treatment was maintained in adults but not children with either the Eisenmenger Syndrome or post-operative PAH [25] However other investigators found that bosentan improved or stabilised NYHA functional class in children [11, 18, 26].\_Growth may be an additional marker of treatment efficacy in children [22]. Using these criteria we found that the children continued to grow but there was no change in the z-scores for height

and weight. Relatively few children were recatheterised but those who were re-studied did not show a change in haemodynamics. Others have reported an improvement, although the absolute changes in pressure and resistance have usually been modest in both children and adults [8, 10, 11]. Given that pulmonary vascular disease is a progressive disease it is reassuring to find that the patients did not show a deterioration in haemodynamics.

In the course of the present study, 39% of all children started on bosentan monotherapy needed additional sildenafil or epoprostenol or both. About 65% of children with IPAH remained event free at one year and 38% at 2 years, without additional therapy for worsening of symptoms, transplantation, or death. The median time to treatment failure was 18 months. An adult study found that 61% and 44% of patients had not required either prostanoid therapy or transplantation at 1 and 2 years[8], figures not markedly different to our own in children. As expected, the children with congenital heart disease fared better than those with IPAH, only 37% of those on bosentan monotherapy needed additional treatment and the median time to treatment failure was longer, 39.2 and 54.2 months for those with the Eisenmenger Syndrome and post repair pulmonary hypertension respectively. Thus although survival in the 3 diagnostic groups was similar the children with pulmonary hypertension associated with congenital heart disease needed less additional therapy to maintain improvement than did those with IPAH.

In summary, these studies indicate that bosentan alone or with other pulmonary hypertensive treatment can be effective in the long term management of children with pulmonary arterial hypertension. For at least the first 3 years the results of treatment

are at least as good as those in adults, and the children have been followed up for longer, up to 5 years [8]. Side effects are unusual but monthly liver function tests remain mandatory. Pulmonary vascular disease is however, a progressive disease and since the majority of our patients with IPAH and a significant proportion of those with associated PAH needed additional medication to sustain improvement these children need to be followed up very closely indeed. The number of children followed up for 5 years is relatively small but it does appear that in IPAH survival falls significantly after 3 years of treatment, despite escalation of therapy. This emphasises the need for a proactive, aggressive approach to the management of IPAH in children with combination therapy, treating the three signalling pathways known to be involved in the pathobiology of pulmonary vascular disease.

Based on our experience we would recommend the following:

i) Close follow-up supervision. ii) Starting combination therapy at presentation. In patients with IPAH dual oral therapy can be used if in functional classes I, II or relatively well in class III. All class IV and severely symptomatic class III children should receive intravenous epoprostenol and ideally bosentan and sildenafil. In a less critical situation the family usually needs a few weeks on combined oral therapy to begin to adjust to having a very sick child whom they had previously thought normal, before starting intravenous therapy. Quality of life, for the child and the family is extremely important, particularly when the disease cannot be cured.

We need new drugs which target deranged signalling pathways. This will entail designing clinical trials specifically for children to determine safety, efficacy and optimum dosing criteria. The need for long term follow up to detect any detrimental

effect on the growing child is self evident and applies to all existing and all new drugs used to treat pulmonary hypertension in children.

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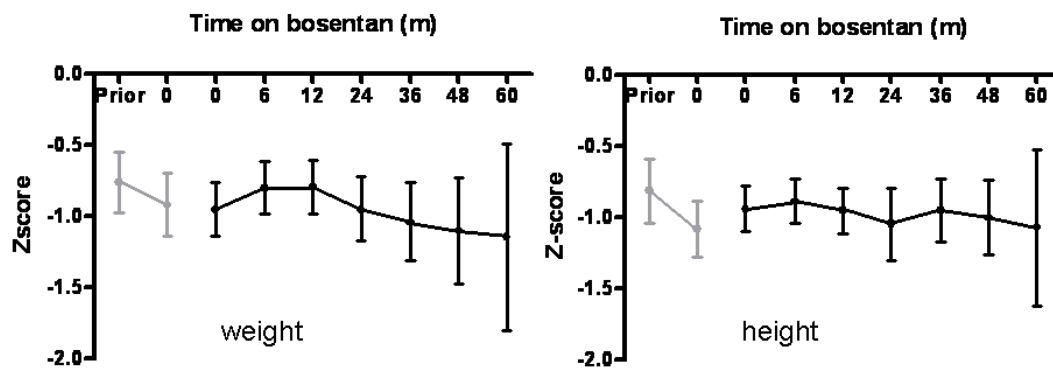
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Figure legends

**Figure 1.** Mean height and weight z-scores throughout the study period showing no significant change with treatment. Values for the cases assessed prior to the start of treatment are shown in grey.

Figure 1



**Figure 2.** WHO Functional Class a) mean value (with SD) approximately 6 months prior to instituting bosentan therapy, at the start of bosentan treatment (time 0) and after 6,12 and 36 months. Values for the cases assessed prior to the start of treatment are shown in grey.

b) The percentage of cases in each WHO Functional Class.

c) The percentage of cases improving, worsening or staying the same with time

Figure 2a

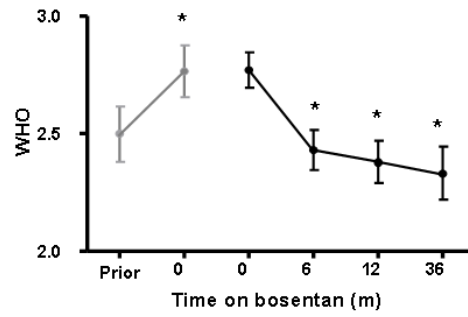


Figure 2b

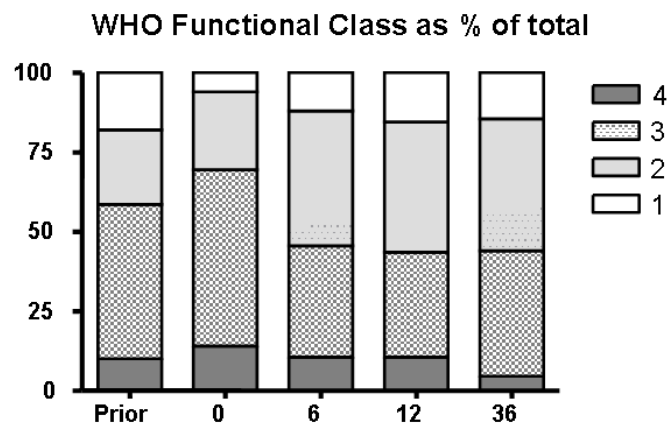
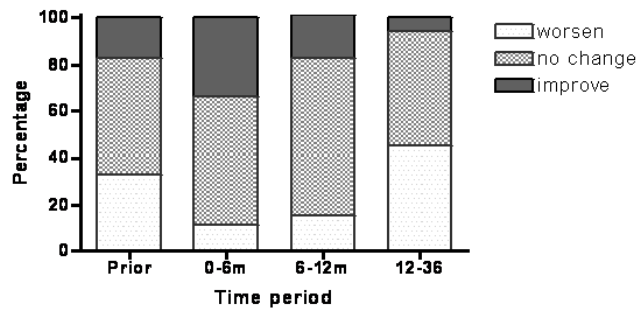


Figure 2c



**Figure 3.** 6 minute walk distance a) % of predicted walk distance for age prior to starting treatment and during treatment with bosentan. Values for the cases assessed prior to the start of treatment are shown in grey.

b) The % 6 minute walk distance by diagnostic group.

Figure 3a

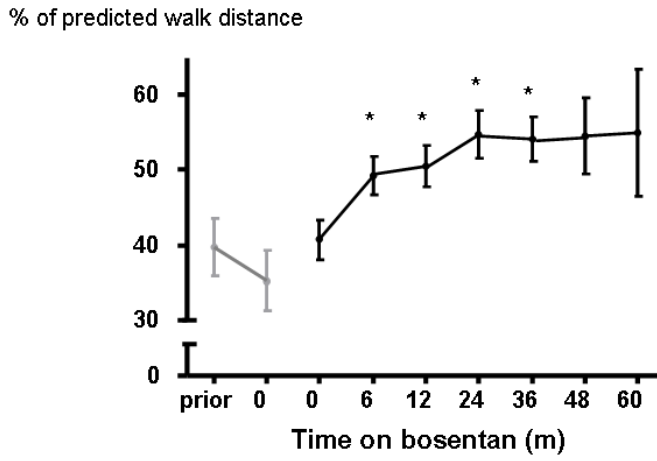
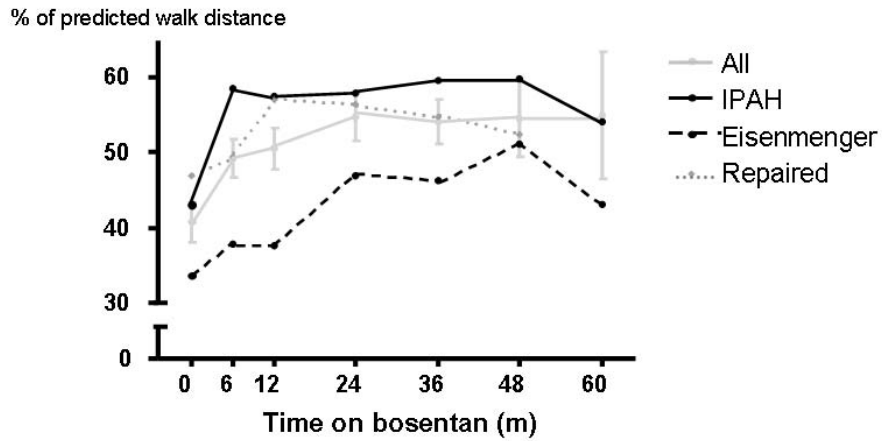


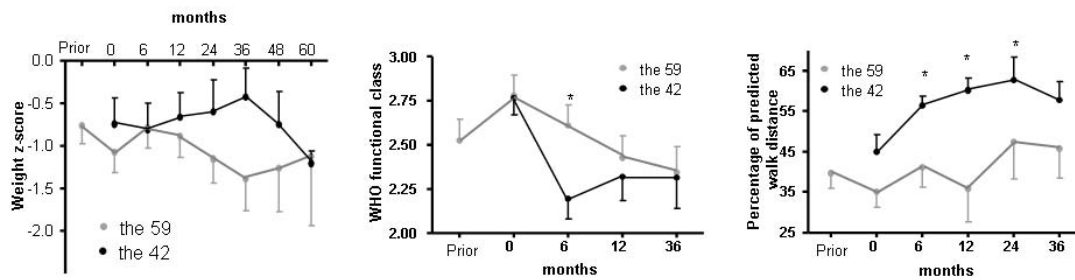
Figure 3b





**Figure 4.** Comparison of the 59 cases studied 4.9 months before starting bosentan and the remaining 42 cases for weight centile, WHO and % 6 minute walk distance at start of bosentan therapy and during follow up.

Figure 4



**Figure 5.** a) Kaplan Maier for treatment success for the patients with IPAH, repaired congenital heart disease and Eisenmenger Syndrome. The median time to treatment failure was 18 months for IPAH, 39.2 months for those with the Eisenmenger Syndrome and 54.2 months for the repaired cases ( $p=0.03$  log rank test for trend).and b) the survival for these three groups of patients with transplantation as a censoring event.

Figure 5a

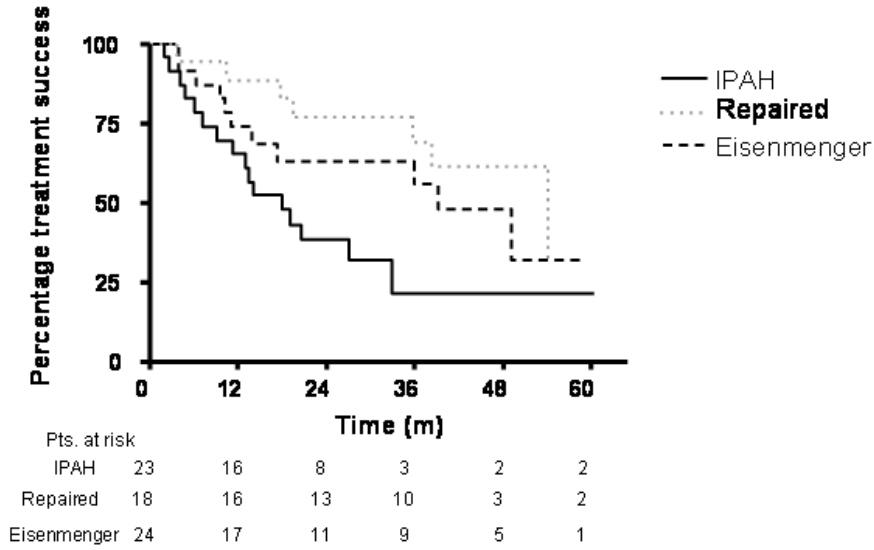
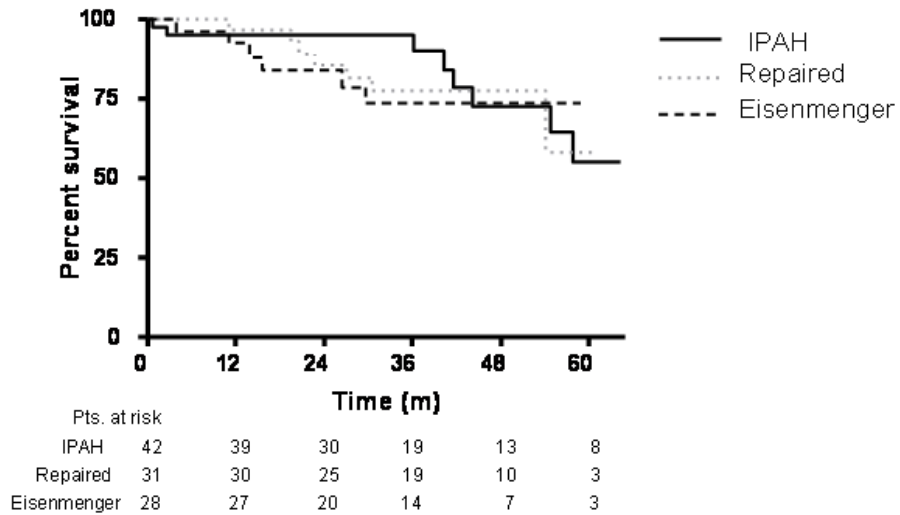


Figure 5b



**Table 1.** Demographic, clinical and haemodynamic characteristics at start of bosentan treatment in children with IPAH and PAH Associated with Congenital Heart Disease

	Total	IPAH	Repaired	Eisenmenger	P values between groups
<u>Demographic</u>					
Subjects (n)	101	42	31	28	
Female %	58	62	51	61	0.66
Trisomy 21(%)	20 (20)	2 (5)	3 (10)	15 (54)	<0.001
Age at Presentation (y)	8.9(5.3)	7.4(5.4)	8.7(5.1)	11.5(4.5)	0.005
Starting bosentan(y)	9.7(5.5)	8.0(5.7)	9.6(5.0)	12.3(4.7)	0.004
Number (%) on monotherapy	67(67)	24(57)	20(64)	23(82)	
<u>Clinical</u>					
Mean weight z-score (SD)	-0.95(1.8)*	-0.66 (1.77)*	-1.71 (1.92)*	-0.49 (1.42)	0.02
Mean height z-score (SD)	-0.94 (1.5)*	-0.72 (1.45)*	-1.44 (1.46)*	-0.65 (1.54)*	0.12
WHO I/II/III/IV(mean)	6/25/56/14(2.8)	2/8/25/7(2.9)	4/9/12/6(2.6)	0/8/19/1(2.8)	0.43
6MWD % normal	40.69(18.7)	43 (21.03)	46.93(18.9)	33.5(14.4)	0.08
<u>Haemodynamics</u> (Mean and SD)					
	(n=79)	(n=40)	(n=21)	(n=18)	
RAP (mmHg)	7.6(3.4)	6.9 (3.5)	8.9(3.4)	8.1(2.2)	0.05
mPAP (mmHg)	56.4(21.4)	60.9(24.1)	45(17.9)	61.3(11.3)	0.003
mPAP (mmHg) on iNO	53.13(19.5)	56.2(21)	42.5(16.9)	60.9(11.8)	0.0066
PVRI (U.m <sup>2</sup> )	21.07(13.8)	22.5(13.8)	14.2(10.1)	28.12(15.2)	0.003
PVRI (U.m <sup>2</sup> ) on iNO	17.37(12.6)	17.6(11.7)	11.3(7.1)	27.07(16.5)	0.003
Qp	2.68(1.19)	2.68(1.13)	2.38(0.55)	2.91(1.8)	0.90
Qp on iNO	3.36(2.36)	3.46(2.45)	3.4(2.6)	2.94(1.93)	0.62

Data are presented as mPAP = mean pulmonary artery pressure, PVRI = pulmonary vascular resistance index. iNO = inhaled nitric oxide  
\* significantly different to normal