INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease that is characterised by a mean pulmonary arterial pressure of ≥25 mmHg, pulmonary capillary wedge pressure of <15 mmHg and normal or reduced pulmonary vascular resistance.1

The untreated life expectancy of PAH in children is reported to be 12 months, much worse than the 2.8 years that would be typical for adults with PAH.2

The treatment of children with PAH is frequently challenging, due to the limited evidence on dosages compared with adult treatment, the approachability of treatment and the difficulties in giving continuous prostacyclin therapy.3

Previous studies have reported on the efficacy and safety of bosentan as a treatment for pediatric PAH.1,4 A paediatric formulation of bosentan has been developed and the pharmacokinetics were assessed and safety and tolerability demonstrated that the new formulation of pediatric bosentan was generally well tolerated in children with PAH.5

Here we present the results from FUTURE-2, the single-arm extension of FUTURE-1.

METHODS

Study design

FUTURE-2 was an extension study of FUTURE-1, a 12-week, placebo, randomized, single-arm study.3,6 The aim of the FUTURE-2 study was to assess the long-term safety and tolerability of the formulation of bosentan’s form of bosentan. The study design is shown in Figure 1. The maintenance dose of bosentan was 4 mg·kg⁻¹·d⁻¹, if tolerated, or dose reduced down titrated to 2 mg·kg⁻¹·d⁻¹. Dose adjustments (i.e., up-titration to 4 mg·kg⁻¹·d⁻¹ and down titration to 2 mg·kg⁻¹·d⁻¹) could be performed at any time deemed necessary by the investigator.

The end of study occurred when:

- The investigator or patient decided to permanently discontinue the study drug.
- Bosentan was commercially available as a pediatric formulation in the country of the study patient.
- The study patient reached the age of 12.

Addition of a pediatric formulation, other than endothelin receptor antagonists (ERAs) or sildenafil, were permitted during the study in the case of PAH worsening.

RESULTS

Patient disposition and demographics
Thirty-six patients were enrolled in FUTURE-1.1-5 In the previous bosentan-treated subgroup at the start of the study treatment and 21 were in the non-bosentan-alone subgroup. All 36 patients received bosentan dose 11-30.

Of the 36 patients who enrolled in FUTURE-1, two did not complete FUTURE-1 and one did not enter FUTURE-2, therefore 33 patients continued FUTURE-2 (Figure 2).

19 patients (52.8%) discontinued from the study for administrative reasons, or due to withdrawal of consent, death, disease progression, AEs, lung transplantation, or treatment failure.

Patient demographics are given in Table 1.

- At baseline in FUTURE-1 more females than males were enrolled (58.3% vs. 41.7%) and the mean (SD) age was 6.8 (2.7) years.
- The majority of patients (88.1%) had idiopathic PAH and the mean (SD) duration of PAH from diagnosis was 31.6 (20.3) months.
- Most patients (75.0%) were treated with at least one concomitant medication; the most common medications were anticoagulants (e.g., warfarin) and phosphodiesterase-5 inhibitors.

Table 1. Baseline demographics of patients at the start of FUTURE-1.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Previously treated (n=15)</th>
<th>Previously not treated (n=21)</th>
<th>All patients (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (53.3%)</td>
<td>17 (80.9%)</td>
<td>25 (69.4%)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (46.7%)</td>
<td>4 (19.1%)</td>
<td>11 (30.6%)</td>
</tr>
<tr>
<td>Age (years):</td>
<td>6.8 ± 2.7</td>
<td>6.8 ± 3.0</td>
<td>6.8 ± 3.0</td>
</tr>
<tr>
<td>Weight (kg):</td>
<td>21.3 ± 4.7</td>
<td>23.1 ± 9.8</td>
<td>22.3 ± 8.0</td>
</tr>
<tr>
<td>Height (m):</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
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<tr>
<td>Concomitant medications at baseline, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anticoagulants</td>
<td>10 (66.7%)</td>
<td>17 (80.9%)</td>
<td>27 (75.0%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>3 (20.0%)</td>
<td>11 (52.4%)</td>
<td>14 (38.9%)</td>
</tr>
<tr>
<td>Inhaled steroid</td>
<td>2 (13.3%)</td>
<td>3 (14.3%)</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>5 (33.3%)</td>
<td>5 (23.8%)</td>
<td>10 (27.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (20.0%)</td>
<td>5 (23.8%)</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>Other anticoagulants</td>
<td>2 (13.3%)</td>
<td>4 (19.0%)</td>
<td>6 (16.7%)</td>
</tr>
<tr>
<td>Other medications</td>
<td>6 (40.0%)</td>
<td>10 (47.6%)</td>
<td>16 (44.4%)</td>
</tr>
</tbody>
</table>

Table 2. Treatment-emergent adverse events occurring in ≥10% of patients.

1. The Kaplan–Meier estimate of not having experienced clinical worsening of PAH was 78.9% (95% CI 60.7–89.3%) at 2 years and 73.6% (95% CI 53.8–88.6%) at 4 years in all patients (Figure 3).

OUTCOMES measures

- Safety and tolerability were assessed by adverse events (AEs), serious AEs (SAEs), death and clinical laboratory assessments.
- Efficacy was assessed in an exploratory manner. Among the exploratory efficacy endpoints, time to worsening of PAH, defined as death, disease progression, lung transplantation, or treatment failure, was assessed.

Statistical analysis

- All the analyses were conducted on the pooled data of FUTURE-1 and FUTURE-2, including all patients who received dose 1-30 of bosentan.
- No formal statistical hypothesis was set for this single-arm extension study.
- Descriptive statistics are displayed for the safety and efficacy endpoints.

Serious adverse events and deaths

- 6 treatment-related deaths (8.3%) occurred in previously bosentan-treated patients vs. 42.9% of previously bosentan-naive patients.
- The most frequent SAEs were device-related infection (in patients who were receiving an intravenous infusate) and PAH/PVR both occurring in ≥3.9% patients.
- Three SAEs were thought to be related to bosentan; two incidences of PAH worsening and a case of idiopathic PAH.

- For the patient with autoimmune hepatitis, the diagnosis was preceded by an increase in liver enzymes to > the upper limit of normal, which remained elevated following a reduction in the dose of bosentan.
- The patient was subsequently diagnosed with autoimmune hepatitis and bosentan treatment was stopped.

Time to PAH worsening

- The Kaplan–Meier estimate of not having experienced clinical worsening of PAH was 78.9% (95% CI 60.7–89.3%) at 2 years and 73.6% (95% CI 53.8–88.6%) at 4 years in all patients (Figure 3).

CONCLUSIONS

- Most of the AEs that occurred during this study are those commonly present in any pediatric population, expected in PAH patients, or were expected in the underlying disease.
- AEs such as chest pain, fatigue, and syncope were likely to be due to the underlying disease.
- Autologous hematopoiesis has been previously observed with bosentan, but as disturbances to liver function due to treatment with bosentan can be unpredictable, monitoring of liver function is mandatory.

- The long-term use of the pediatric formulation of bosentan in this study was generally well tolerated, and presented no unexpected safety concerns; the overall safety profile was comparable to that seen with the adult formulation.4

References