Application of the criteria for satisfactory clinical response to riociguat treatment of patients for pulmonary arterial hypertension (PATENT-1 and PATENT-2)

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Background

• Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by elevated pulmonary vascular resistance that can result in death due to right heart failure.1

• Riociguat, a soluble guanylate cyclase (sGC) stimulator, has demonstrated robust efficacy in patients with PAH.

• In the 12-week, Phase II, placebo-controlled PATENT-1 study, riociguat significantly improved 6-minute walking distance (6MWD) and a range of secondary endpoints in treatment-naive and pretreated patients with PAH.1 2

Methods

Study design

• In PATENT-1, patients received riociguat, individually adjusted to a maximum of 2.5 mg three times daily (tid), or riociguat individually adjusted to a maximum of 1.5 mg tid (exploratory group).

• Patients who completed the 12-week PATENT-1 study without any ongoing riociguat-related serious adverse events were eligible to participate in the PATENT-2 long-term extension study.

• Upon entry into PATENT-2, patients underwent an 8-week, double-blind, dose-adjustment phase (Figure 1).

• Patients originally randomized to riociguat 2.5 mg maximum continued on their optimum dose while receiving sham dose adjustment.

• Patients originally randomized to placebo or riociguat 1.5 mg maximum were adjusted to their optimum dose up to 2.5 mg tid.

Clinical worsening was defined as the first occurrence of any of the following events: death, heart failure, transplantation, atrial fibrillation, hospitalization due to worsening of PAH, start of new specific PAH treatment or modification of existing pre-existent treatment, persistent decrease of >15% from baseline in 6MWD, and persistent worsening of WHO FC.1

A Kaplan-Meier analysis was used to assess the effect of achieving components of the SCR endpoint on long-term outcomes in PATENT-2.

The riociguat 2.5 mg–maximum and 1.5 mg–maximum groups were pooled for these analyses.

• Patients with missing 6MWD or WHO FC values were excluded.

Results

Satisfactory clinical response: PATENT-1

• SCR status at Week 12 was determined for 410 of the 440 patients enrolled in PATENT-1 (291 in the pooled riociguat group and 119 in the placebo group).

• Overall, 30% of patients in the pooled riociguat group achieved an SCR on treatment at Week 12 compared with 16% in the placebo group (Figure 2).

• As shown in Figure 3, the odds ratio (OR) of achieving an SCR with riociguat versus placebo was 2.2 (95% confidence interval 1.3–3.9).

• This effect was generally consistent across patient subgroups, although patients with PAH associated with connective tissue disease showed a less favorable response when compared with patients with primary PAH.

• Overall, 44% of patients in the former riociguat group and 33% of patients in the former placebo group achieved an SCR (Figure 4).

• In the pretreated subgroup, 48% of former riociguat patients and 40% of former placebo patients achieved an SCR.

• In the treatment-naive subgroup, the proportions were 40% and 26%, respectively.

• The effect was less pronounced in the pretreated subgroup (22% with riociguat versus 10% with placebo).

• The proportion of patients achieving SCR was 15% in the former placebo group and 11% in the former riociguat group.

Association of SCR with long-term outcomes in PATENT-2

• Figure 5 shows long-term clinical worsening-free survival in patients achieving or not achieving components of the SCR (<10% improvement from baseline in 6MWD and/or improvement to or maintenance of WHO FC II) after 24 weeks of riociguat therapy.

Conclusions

• Riociguat increased the proportion of patients who met SCR criteria compared with placebo at Week 12 in PATENT-1, with further increases observed in both former riociguat and former placebo patients during PATENT-2.

• The proportion of treatment-naive patients achieving an SCR after 24 weeks of riociguat treatment in PATENT-2 Week 12: 48% was similar to that previously reported for the treatment-naive group at Week 24 of the AB Initio study (34%)2.

• These data further support the value of using the SCR endpoint as a measure of efficacy in patients with PAH.

References


Acknowledgments

The PATENT studies were funded by Bayer Pharma AG. Editorial support was provided by Adelphi Communications Ltd, supported by Bayer Pharma AG.


Figure 2. Number of patients achieving an SCR at Week 12 of PATENT-1.

Table 1. Patients achieving individual components of the SCR at Week 12 of PATENT-1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Overall population</th>
<th>Treatment-naive</th>
<th>Pretreated</th>
</tr>
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<tbody>
<tr>
<td>Improvement to or maintenance of WHO FC I/II</td>
<td>15% (68/440)</td>
<td>21% (53/251)</td>
<td>10% (15/189)</td>
</tr>
<tr>
<td>10% Improvement from baseline in 6MWD</td>
<td>Yes</td>
<td>128 (46/377)</td>
<td>14 (12/189)</td>
</tr>
<tr>
<td>No</td>
<td>282 (330/377)</td>
<td>23 (12/189)</td>
<td>60 (27/377)</td>
</tr>
<tr>
<td>Improvement to or maintenance of WHO FC II</td>
<td>Yes</td>
<td>178 (69/377)</td>
<td>14 (12/189)</td>
</tr>
<tr>
<td>No</td>
<td>292 (330/377)</td>
<td>23 (12/189)</td>
<td>60 (27/377)</td>
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</table>

Table 2. Patients achieving individual components of the SCR at Week 12 of PATENT-2.

<table>
<thead>
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<th>Component</th>
<th>Overall population</th>
<th>Treatment-naive</th>
<th>Pretreated</th>
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<tbody>
<tr>
<td>10% Improvement from baseline in 6MWD</td>
<td>Yes</td>
<td>80 (41)</td>
<td>60 (33)</td>
</tr>
<tr>
<td>No</td>
<td>232 (145)</td>
<td>60 (33)</td>
<td>20 (70)</td>
</tr>
<tr>
<td>Improvement to or maintenance of WHO FC II</td>
<td>Yes</td>
<td>111 (62)</td>
<td>60 (33)</td>
</tr>
<tr>
<td>No</td>
<td>53 (33)</td>
<td>60 (33)</td>
<td>20 (70)</td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier plot showing effect of achieving components of the SCR endpoint on clinical worsening free survival.