Riociguat for Chronic Thromboembolic Pulmonary Hypertension and Pulmonary Arterial Hypertension: First Long-term Extension Data from a Phase II Study

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Rationale

Although management of pulmonary hypertension has improved in recent years, it remains a devastating, life-threatening disease. Riociguat is a novel oral stimulator of soluble guanylate cyclase, a key enzyme in the nitric oxide signaling pathway. Riociguat has demonstrated efficacy and a favorable safety profile in treating chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) in a 12-week trial, but no long-term data have yet been presented. We investigated the long-term safety, tolerability and efficacy of riociguat in patients with CTEPH and PAH.

Methods

Patients with CTEPH or PAH who had enrolled in a 12-week multicenter uncontrolled trial of riociguat (WHO functional class [FC] II/III, mean pulmonary vascular resistance > 300 dyn.s/cm^5 and mean pulmonary arterial pressure > 25 mmHg at baseline) were invited to enter a long-term extension phase (LTE). Riociguat doses were titrated from a starting dose of 1 mg three times daily (t.i.d.) according to systolic blood pressure (range: 0.5-2.5 mg t.i.d.). Assessments (6-minute walking distance [6MWD], FC and safety parameters) were subsequently performed at 3-month intervals.

Results

Of the 78 patients in the 12-week trial, 68 entered the LTE (CTEPH, 41; PAH, 27). At the cut-off date for this analysis, the mean LTE duration was 14.0 ± 6.3 months, 65 patients remained alive and 54 patients remained on riociguat. Riociguat dose during the LTE was 2.5 mg t.i.d. in 73.5-75.0% of patients. In addition to conventional background therapy, 26 patients took endothelin receptor antagonists and 1 patient took iloprost (6 patients took endothelin receptor antagonists at baseline). Peripheral edema (n=12) and nasopharyngitis (n=12) were the most common adverse events, followed by hypotension (n=10), respiratory tract infection (n=8) and syncope (n=7; 3 regarded as drug-related).

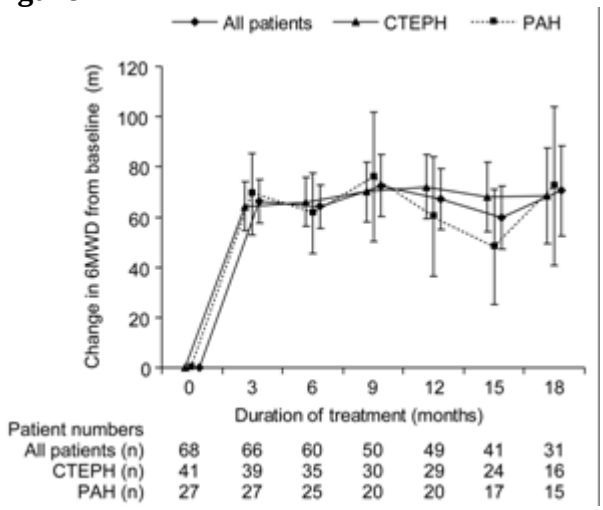
Mean 6MWD improved in the 12-week trial (baseline, 365 m; 12 weeks, 431 m) and was sustained for at least 15 months thereafter (430 m; Figure). The proportion of patients in FC I/II increased from 20.6% at baseline to 47.0% at 12 weeks, and was maintained at 53.2-58.1% during the next 15 months.

Conclusions

This study presents the first long-term data for riociguat. In patients with CTEPH and PAH, riociguat was generally well tolerated, had a favorable safety profile, and caused sustained improvement in 6MWD and FC for at least 15 months. Phase III trials in patients with CTEPH and PAH are ongoing.

This abstract is funded by Bayer HealthCare AG.

Figure 1



Mean improvement in 6MWD by subtype of pulmonary hypertension. Error bars show standard error of the mean. Two patients did not have 6MWD data at 3 months but continued into the extension phase, hence data are available for 66 patients at 3 months. 6MWD, 6-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.