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/cm5 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.

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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.