Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial

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**ABSTRACT:** We assessed the safety, tolerability and preliminary efficacy of riociguat, a soluble guanylate cyclase stimulator, in patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD).

In this open-label, uncontrolled pilot trial, patients received oral riociguat (1.0–2.5 mg t.i.d.) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15). Primary endpoints were safety and tolerability. Secondary endpoints included haemodynamic changes and 6-minute walk distance (6MWD).

Overall, 104 adverse events were reported, of which 25 were serious; eight of the latter were considered drug-related. After 12 weeks of therapy, mean cardiac output increased (4.4 ± 1.5 L/min to 5.5 ± 1.8 L/min), pulmonary vascular resistance (PVR) decreased (648 ± 207 dyn s cm⁻⁵ to 528 ± 181 dyn s cm⁻⁵) and mean pulmonary artery pressure (PAPm) remained unchanged compared with baseline. Arterial oxygen saturation decreased but mixed-venous oxygen saturation slightly increased. The 6MWD increased from 325 ± 96 m at baseline to 351 ± 111 m after 12 weeks.

Riociguat was well tolerated by most patients and improved cardiac output and PVR, but not PAPm. Further studies are necessary to evaluate the safety and efficacy of riociguat in patients with PH-ILD.

**KEYWORDS:** Clinical study, interstitial lung disease, pulmonary hypertension, riociguat, soluble guanylate cyclase
Interstitial lung disease (ILD) represents a heterogeneous group of diseases that share common functional features including a decline in pulmonary compliance and impairment of gas exchange [1-3]. The underlying pathology of ILD is characterised by fibrous remodelling of the pulmonary interstitium which ultimately results in irreversible structural changes and death. There are still no effective therapies for many forms of ILD.

Approximately 30–40% of patients with ILD develop pulmonary hypertension (PH), which contributes significantly to their functional impairment and substantially worsens their prognosis [1, 4-8]. Thus, there is a growing interest in targeting PH in patients with ILD.

Various classes of drugs, including endothelin receptor antagonists, prostanoids and phosphodiesterase-5 (PDE-5) inhibitors [9-11], have beneficial effects in patients with pulmonary arterial hypertension (PAH). Case reports and open-label studies have suggested that some of these drugs might also improve haemodynamics and exercise capacity in patients with PH-ILD [12-15]. A recent placebo-controlled 12-week study of the PDE-5 inhibitor sildenafil in patients with advanced idiopathic pulmonary fibrosis (IPF) failed to show a significant change in 6-minute walk distance (6MWD), although there were beneficial effects on arterial blood gases and carbon monoxide diffusion capacity and health-related quality of life measures [16]. No randomised controlled trials of PAH treatments in the PH-ILD patient population have been published. Consequently, no pharmacological therapy has gained regulatory approval for the specific indication of PH-ILD, and due to the lack of robust data, current PH guidelines discourage the off-label use of PAH-targeting drugs in such patients [3, 17]. Conventional vasodilators are also not recommended in PH-ILD because they may impair gas exchange due to the inhibition of hypoxic
pulmonary vasoconstriction [17]. Therefore, the enrolment of patients in high-quality clinical trials in order to identify new therapeutic options is vital [18].

The development of new classes of drugs for the treatment of PH depends on improved understanding of its pathophysiology. In healthy individuals, endothelial cell-derived nitric oxide (NO) acts on smooth muscle cells to induce vasodilation by increasing production of the second messenger cyclic guanosine monophosphate (cGMP) via activation of the intracellular enzyme soluble guanylate cyclase (sGC) [19, 20]. In PH, production of NO is reduced, resulting in inhibition of sGC activity and depletion of cGMP which can lead to numerous abnormalities including pulmonary vasoconstriction, adverse vascular remodelling and in situ thrombosis [21, 22]. Riociguat is the first of a new class of drugs, the sGC stimulators, designed to both stimulate sGC independently of NO and sensitise the enzyme to low levels of NO, thereby restoring cGMP levels [23]. As a result of its NO-independent action, riociguat could be effective under conditions of NO depletion that restrict the effectiveness of PDE-5 inhibitors.

In a preliminary, non-controlled study in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH), riociguat improved exercise capacity, functional class and pulmonary haemodynamics [24]. Furthermore, in an acute haemodynamic study that included some patients with PH-ILD, riociguat improved haemodynamics without worsening gas exchange [25]. Based on these observations we hypothesised that riociguat could have beneficial effects in patients with PH-ILD. In this pilot trial we primarily assessed safety and tolerability of riociguat in this patient population and studied preliminary effects of the drug on haemodynamics, blood gases and exercise capacity.
METHODS

Study design and patients

This multicentre, open-label, non-blinded, non-randomised, uncontrolled Phase II study was conducted across five centres in Germany. Patients aged ≥18 years diagnosed with any of four types of ILD (IPF, non-specific interstitial lung disease (NSILD), scleroderma or sarcoidosis) and a total lung capacity (TLC) ≤90% of the predicted value (≤80% of the predicted value in patients with scleroderma) were enrolled. Eligible patients also had a mean pulmonary artery pressure (PAPm) >30 mmHg, a pulmonary capillary wedge pressure (PCWP) <15 mmHg and a pulmonary vascular resistance (PVR) >400 dyn s cm⁻⁵, as demonstrated by right heart catheterisation within 3 months prior to the commencement of the study. For at least 3 months before study entry, patients were required to have stable ILD (decrease in forced expiratory volume in one second (FEV₁) <10% and decrease in diffusing capacity of lung for carbon monoxide (DLCO) <15%) and be on stable medication (e.g. no changes in the doses of corticosteroids and/or immunosuppressants, if present, during that time).

The most important exclusion criteria were previous or ongoing treatments with other P(A)H-targeting drugs, including prostanoids, endothelin receptor antagonists or PDE-5 inhibitors. The use of nitrates was also prohibited. Further exclusion criteria included: advanced pulmonary fibrosis indicated by a TLC ≤30% predicted; a PaO₂ <50 mmHg or a PaCO₂ >45 mmHg in room air; other clinically relevant lung diseases including more than mild airflow obstruction (FEV₁/FVC ratio ≤60%); severe congenital abnormalities of the lungs, thorax or diaphragm; left ventricular dysfunction (left ventricular ejection fraction <50%); and symptomatic coronary heart disease.
The study was performed in accordance with the Good Clinical Practice guidelines and the guiding principles detailed in the Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating centres and all patients gave their written informed consent (ClinicalTrials.gov identifier: NCT00694850).

**Procedures**

Riociguat (Bayer HealthCare AG, Germany) was administered orally three times daily (t.i.d.) for 12 weeks, titrated in 0.5 mg increments at 2-week intervals from a starting dose of 1 mg to a target dose of 2.5 mg t.i.d. Systolic blood pressure (SBP) was measured in resting patients one hour before administration of the morning dose of riociguat. The dose was increased if SBP was >100 mmHg, maintained if SBP was 90–100 mmHg and reduced if SBP was <90 mmHg without symptoms of hypotension (such as dizziness or syncope). Riociguat was stopped if SBP was <90 mmHg with clinical signs of hypotension. Re-start of treatment was possible after 24 hours at a reduced dose (–0.5 mg t.i.d.). Riociguat was discontinued permanently if the resting heart rate increased above 120 beats per minute (bpm) or if SBP fell below 80 mmHg. Subjects who tolerated treatment well were enrolled in an ongoing long-term extension study. Interim analysis at 12 months of this ongoing study is presented here.

As this was essentially a safety study, the primary endpoints were safety and tolerability throughout the initial 12-week study period and at 12 months. Vital signs, electrocardiographic findings and laboratory parameters were evaluated every 2 weeks during the initial treatment period and every 3 months thereafter. Laboratory
parameters included blood gases, haematology, clinical chemistry including N-terminal pro-brain natriuretic peptide (NT-proBNP) and urine composition.

The major efficacy outcomes at 12 weeks were the 6MWD, the modified Borg dyspnoea score (at the end of the 6MWD), functional class and quality of life scores (SF-36, EuroQoL). Patients were allowed to use oxygen during all study procedures including the 6-minute walk test, but they were required to maintain the same flow of oxygen throughout the study. Mixed-venous oxygen saturation (SvO₂) and haemodynamic parameters including right atrial pressure (RAP), PAPm and PCWP were measured during right heart catheterisation at baseline and week 12. Peripheral oxygen saturation (SaO₂) was measured by pulse oximetry, cardiac output (CO) was measured by thermodilution and systemic arterial pressure was measured non-invasively. Systemic vascular resistance (SVR), PVR and cardiac index were calculated by standard formulae. 6MWD was the only efficacy outcome assessed during the long-term extension period.

**Statistical methods**

Statistical analyses undertaken in this small open-label, uncontrolled pilot trial were largely descriptive, and there was no formal statistical sample size estimation. Safety analyses were based on those subjects who received at least one dose of study medication. At the end of the 12-week study period, 95% confidence intervals (CIs) were calculated for changes in efficacy parameters from baseline. Efficacy analyses were performed only in patients who completed the study (per-protocol population). No imputations have been made. Efficacy results were expressed descriptively for
the extension study. Results are given as mean ± standard deviation (SD) unless stated otherwise.

RESULTS

Patient demographics and drug dosing

A total of 23 patients were enrolled in this study, 22 of whom received at least one dose of riociguat and were valid for safety or intention to treat (ITT) analysis (fig 1). Of these 22 patients, their mean age was 60.5 years (range: 33.0–80.0), mean body mass index (BMI) was 26 ± 4 kg/m², 14 were men (63.6%) and all were Caucasian (table 1). Concomitant medications were being used by all patients, the most common of which were corticosteroids (81.8%) and proton-pump inhibitors (59.1%). Of the 22 subjects receiving study drug, all had PH: 13 (59.1%) had a diagnosis of IPF-associated PH; five (22.7%) had NSILD-associated PH; three (13.6%) had sarcoidosis-associated PH; and one (4.5%) had scleroderma-associated interstitial lung disease and PH.

At the end of the 12-week study, 14 (63.6%) subjects were receiving riociguat 2.5 mg t.i.d., three subjects were treated with 2.0 mg t.i.d. and one received 1.5 mg t.i.d. The final total daily doses of riociguat for all subjects, including those who discontinued during the first 12 weeks and those who continued into the 12-month extension, were 0.5 mg t.i.d. in one subject, 1.0 mg t.i.d. in two subjects, 1.5 mg t.i.d. in two subjects, 2.0 mg t.i.d. in four subjects and 2.5 mg t.i.d. in 13 subjects.

Safety

Discontinuations
In the initial 12-week phase, four subjects discontinued therapy permanently due to AEs: leg oedema, relapsing syncope, intense gastroenteritis/leg oedema and progression of ILD. Two of these withdrawals were considered related to the study drug (syncope and intense gastroenteritis/leg oedema, respectively). Eighteen subjects completed 12 weeks of treatment and 15 entered the long-term extension phase. During the long-term extension, a further six subjects discontinued therapy permanently: one patient died from disease progression and respiratory failure, one patient underwent lung transplantation, two withdrew due to AEs (increasing dyspnoea, leg oedema); and two for unspecified reasons. The case of increasing dyspnoea was considered to be potentially related to study medication by both investigator and sponsor. The patient in question had IPF-associated PH and it could not be determined whether clinical worsening was due to disease progression or due to study medication. The patient who underwent lung transplantation died shortly after the procedure (9 days after transplantation and 17 days after discontinuation of riociguat). No other patient underwent lung transplantation during the study period. Both deaths were considered unrelated to riociguat by the investigators and the sponsor.

Hypotension was observed in two subjects (9.1%): no case of hypotension led to permanent discontinuation of riociguat. One additional subject had an episode of syncope, which led to permanent discontinuation of the study drug after completion of the 12-week main phase of the study.

**Adverse events**

Overall, 104 adverse events (AEs) were reported across the 22 subjects during the 12-week treatment period and the extension phase combined. Of these, 86 were considered treatment-emergent (all events post-baseline assessment) and
approximately 70% were considered drug-related. Table 2 shows the AEs reported by ≥2 patients (approximately 10% of the population). The most frequently reported drug-related AEs were dyspnoea (n=6 [27.3%]), peripheral oedema (n=6 [27.3%]), dyspepsia (n=3 [13.6%]), headache (n=3 [13.6%]) and feeling hot (n=3 [13.6%]).

**Serious adverse events**

Overall, 16 subjects experienced 25 SAEs. These included dyspnoea (n=4), pancytopenia (n=2), right ventricular failure, chest pain, bronchitis, diverticulitis, hyponatraemia, hypokalaemia, peripheral oedema, syncope (n=2), progression of ILD, progressive massive fibrosis, pulmonary fibrosis (n=2), viral-triggered exacerbation of lung fibrosis, respiratory disorder, coronary artery disease, closed perforation of a gastric ulcer and respiratory failure (n=2). A total of eight serious AEs were considered possibly related to study drug: syncope (n=1), dyspnoea (n=3); pancytopenia (n=2); respiratory disorder (n=1); and respiratory failure (n=1).

**Laboratory parameters and QT time**

Changes in laboratory parameters including haematology, clinical chemistry, and urine composition were infrequent and none gave any indication of being related to study medication (data not shown). Serum NT-proBNP did not change from baseline (1061.6 ± 1511.9 pg/mL at baseline [n=19] vs 1227.6 ± 1352.0 pg/mL [n=16] at week 12). No untoward effects on QTc duration were evident during the study.
**Haemodynamics**

Haemodynamic results are described below as means ± SD for patients with an assessment at baseline and at least once thereafter (n=15). Individual patient data for CO, PVR and PAP\textsubscript{m} are shown in figure 2.

Compared with baseline, CO increased from 4.4 ± 1.5 L/min to 5.5 ± 1.8 L/min (difference: +1.2 ± 1.0 L/min; 95% CI: 0.6 to 1.8) and cardiac index from 2.4 ± 0.8 L/min/m\textsuperscript{2} to 3.0 ± 1.1 L/min/m\textsuperscript{2} (difference: +0.7 ± 0.7 L/min/m\textsuperscript{2}; 95% CI: 0.3 to 1.0) at week 12. Heart rate increased from 79 ± 14 bpm at baseline to 86 ± 16 bpm at week 12 (difference: +7 ± 12 bpm; 95% CI: 1 to 14).

Between baseline and week 12 (in those patients who had at least one post-baseline assessment), PVR decreased from 648 ± 207 dyn s cm\textsuperscript{-5} to 528 ± 181 dyn s cm\textsuperscript{-5} (difference: -120 ± 93 dyn s cm\textsuperscript{-5}; 95% CI: -174 to -66) and SVR from 2057 ± 808 dyn s cm\textsuperscript{-5} to 1324 ± 278 dyn s cm\textsuperscript{-5} (difference: -821 ± 607 dyn s cm\textsuperscript{-5}; 95% CI: -1787 to 145). This resulted in an increase in the PVR/SVR ratio from 0.31 at baseline to 0.40 after 12 weeks. PAP\textsubscript{m} was virtually unchanged (40 ± 10 mmHg at baseline vs 41 ± 7 mmHg at week 12; difference: +1 ± 10 mmHg; 95% CI: -5 to 6). SBP fell from 139 ± 14 mmHg to 130 ± 16 mmHg (difference -9.3 ± 19.2 mmHg; 95% CI: -19.93 to 1.33).

**Blood gases**

The full data set from haemodynamic measurements and blood gas analyses is shown in table 3. \( \text{PaO}_2 \) decreased by 7 ± 12 mmHg (95% CI: -13 to -1) at 12 weeks and by 3 ± 12 mmHg at 12 months. \( \text{PaCO}_2 \) decreased by 3 ± 2 mmHg (95% CI: -4 to
-2) at 12 weeks and increased by 1 ± 2 mmHg at 12 months (Fig 3). SvO₂ showed a slight improvement between baseline and week 12 (65 ± 6% to 67 ± 7%; difference: +2 ± 4%; 95% CI: 0 to 4).

Pulse oximetry

SaO₂ was measured by pulse oximetry. SaO₂ decreased by 1 ± 5% (95% CI: -4 to 1) at 12 weeks and 0 ± 2% at 12 months from a baseline value of 93.7 ± 3.1%.

Functional class, exercise capacity and quality of life

The 6MWD increased slightly to 351 ± 111 m after 12 weeks, from a corresponding baseline of 325 ± 96 m (n=17) (difference: +25 ± 64 m; 95% CI: -8 to 58). As shown in figure 4, most patients experienced further improvements in 6MWD during follow-up. A single subject was removed from the analysis at 12 weeks as the 6MWD could not be conducted properly.

Mean changes in modified Borg scores ranged from -0.2 to +0.5 during the initial 12-week trial. The descriptive statistics of the modified Borg score showed no relevant change compared with baseline overall (data not shown).

At baseline, 19 subjects were in WHO functional class III and three were in functional class IV. In 16 of the 18 subjects available at week 12, functional class remained unchanged. One patient improved to functional class II and one patient worsened to functional class IV.
At 12 weeks the overall EuroQol EQ-5D scores showed no relevant changes compared with baseline. In most subjects (58.8 to 82.4%), the individual scores (for mobility, self-care, usual activities, pain/discomfort or anxiety/depression) remained unchanged and fewer than 30% of subjects showed an improvement or worsening in any score.

The SF-36 scale assessment did not indicate relevant changes between baseline and week 12.

**DISCUSSION**

The primary objective of the current pilot study was to assess the safety and tolerability of riociguat in patients with PH-ILD. Riociguat was well tolerated by most patients with the incidence and nature of AEs generally similar to previous clinical studies of the drug [24, 25]. Only two subjects during the initial 12-week phase of the study and one subject during the long-term extension phase discontinued treatment prematurely because of side effects considered related to the study drug by both the investigator and sponsor. The proportions of subjects who reported at least one AE or serious AE are not unusual for a serious condition such as PH-ILD. The absence of a placebo group makes it difficult to distinguish between disease-related and drug-related AEs. Eight serious AEs were considered by the investigators potentially related to study drug and six of these (syncope, respiratory disorder, respiratory failure and three cases of dyspnoea) might be expected in PH-ILD. Two cases of severe pancytopenia were reported. One subject received long-term oral cyclophosphamide; stopping the immunosuppressive treatment resulted in the pancytopenia being no longer clinically relevant. The other subject was treated with
azathioprine concomitantly to the study drug. Prior to the study, long-term treatment with azathioprine had been disrupted in this patient due to observed pancytopenia. Both cases recovered without riociguat dose reduction or discontinuation. The majority of the subjects who completed the study were up-titrated to the target dose of 2.5 mg t.i.d. without serious AEs and no cases of hypotension led to permanent discontinuation of study drug. This trial did not reveal any new safety concerns with riociguat.

In this study riociguat was associated with decreases in PVR and SVR, but the latter effect was somewhat greater, resulting in an increased PVR/SVR ratio. These observations suggest that the predominant effect of riociguat in PH-ILD might have been systemic rather than pulmonary vasodilation. This effect may explain the considerable increase in CO (from 4.4 to 5.5 L/min between baseline and 12 weeks). It is notable that PAPm was virtually unchanged overall despite the reduction in PVR. In some patients, a flow-mediated increase in PAPm, consequent on the higher CO, may have offset the effects of pulmonary vasodilation. It is unclear whether the overall workload of the right ventricle was increased or decreased; this question is of importance and deserves further study. The same is true for the left ventricle as patients with chronic lung disease often have impaired left ventricular function [26]. Systemic vasodilation might reduce left ventricular afterload but the increase in CO might add to the left ventricular workload, the net result again being uncertain.

The relatively pronounced systemic vasodilation with riociguat in subjects with PH-ILD may explain the different haemodynamic effects seen in the present trial compared with those reported for patients with PAH and CTEPH [24]. Cardiac index was increased to a greater extent in the present study than in patients with PAH (0.4 (range: 0.2–0.8) L/min/m²) or CTEPH (0.4 (range: 0.2–0.8) L/min/m²). As explained
above, a flow-mediated increase in PAP_{m} as a consequence of the increased CO may explain why the effect on this parameter was variable, with some subjects even showing an increase in PAP_{m}. By contrast, in PAH and CTEPH patients, riociguat lowered PAP_{m} (by 6 mmHg and 4 mmHg, respectively) and reduced the PVR/SVR ratio (by 8% and 5%, respectively). These observations highlight the possibility of different haemodynamic effects of riociguat in different patient populations.

The effects of riociguat on gas exchange were as expected. There was a small decrease in arterial oxygen saturation after 12 weeks. At the same time, SvO_{2} increased slightly owing to the increased CO. At 12 months PaO_{2}, PaCO_{2} and SaO_{2} showed small changes compared with baseline, but once again, this observation should be viewed with caution because of the small sample sizes.

The positive impact of riociguat on CO did not translate into substantial clinical improvements. There was a slight increase in 6MWD at 12 weeks and a more pronounced increase at 12 months in patients remaining on riociguat over that time, which, given the lack of a control group and the fairly high number of drop-outs, should not be overemphasised especially as functional class remained unchanged in almost all patients.

The ILD patients selected in the present study were a subgroup that may be considered likely to respond to PH-targeted therapy. The functional impairment of patients with mild-to-moderate pulmonary fibrosis but moderate-to-severe PH may be linked to ventilatory limitation and, to a greater extent, haemodynamic compromise. Thus, there are several explanations for the lack of a substantial functional improvement in the present study: (i) the rationale may be wrong and these patients are unlikely to benefit functionally from PH-targeted therapy regardless of haemodynamic improvements; (ii) riociguat may not be the ideal drug
for these patients, at least not in the doses administered during this study; (iii) the study was too small, too heterogeneous and too short to demonstrate a meaningful clinical benefit; and (iv) riociguat may only be effective in certain subpopulations. These explanations and views will be explored in further clinical studies.

The present study has several limitations. The patient population was small and heterogeneous, there was no control group, there were several drop-outs, and the observation time of the main study was short (12 weeks). Nonetheless, this was a pilot trial primarily designed to assess safety, and it represents the only trial in PH-ILD with invasive haemodynamic assessments at baseline and follow-up. Despite its limitations, the current study highlights the need for a better understanding of the interplay between the haemodynamic, physiological and clinical effects of a drug, and raises important questions about the endpoints in future trials in the PH-ILD population. Short-term changes in haemodynamics or blood gases are not sufficient to predict the effects of treatment on functional capacity or long-term outcomes. Only an adequately powered long-term trial addressing morbidity and mortality endpoints will provide the data needed to answer these questions and we should remain reluctant to use PH-targeting drugs in patients with chronic lung disease outside the setting of clinical trials until such data are available.

In conclusion, the results of this pilot trial indicate that riociguat appears to be well tolerated by the majority of patients with PH-ILD. It is associated with a substantial increase in CO and reductions in SVR and PVR, and may have the potential to improve exercise capacity in some patients. Larger controlled studies are warranted to further investigate the safety, impact on gas exchange, dosing and efficacy of riociguat in this patient population. Such studies might also increase our
understanding of PH-ILD, a condition which has been inadequately investigated in clinical trials.

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REFERENCES:


TABLE 1. Baseline demographics and clinical characteristics of the patients under study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total study population (n=22)</th>
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<tbody>
<tr>
<td>Age (years), mean (range)</td>
<td>60.5 (33.0–80.0)</td>
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<tr>
<td>White ethnicity, n (%)</td>
<td>22 (100.0)</td>
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<tr>
<td>Male sex, n (%)</td>
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<td>BMI (kg/m²), mean (SD)</td>
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<td>WHO functional class</td>
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<tr>
<td>III, n (%)</td>
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<td>IV, n (%)</td>
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<td>6-minute walk distance (m), mean (SD)</td>
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<td>Underlying disease</td>
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<td>Idiopathic pulmonary fibrosis, n (%)</td>
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<td>Non-specific interstitial lung disease, n (%)</td>
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<td>TLC (% predicted), mean (SD)</td>
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<td>FVC (% predicted), mean (SD)</td>
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<td>FEV₁ (% predicted), mean (SD)</td>
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<td>Haemodynamics and blood gases</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg), mean (SD)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn·s·cm⁻⁵), mean (SD)</td>
<td>656 (201)</td>
</tr>
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</table>
Cardiac output (L/min), mean (SD) 4.3 (1.4)

Systolic blood pressure (mmHg), mean (SD)* 136 (16)

Heart rate (beats per minute), mean (SD)† 78 (14)

SaO₂ (%), mean (SD) 94 (3)

SvO₂ (%), mean (SD)† 62 (12)

PaCO₂ (mmHg), mean (SD) 39 (7)

BMI: body mass index; DLCO: diffusing capacity of lung for carbon monoxide; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PaCO₂: arterial partial carbon dioxide pressure; SaO₂: peripheral oxygen saturation; SD: standard deviation; SvO₂: mixed-venous oxygen saturation; TLC: total lung capacity; WHO: World Health Organisation.

*data available for 20 patients.

†data available for 21 patients.
TABLE 2. Treatment-emergent and drug-related adverse events experienced by ≥2 patients during the 12-week treatment or continuation phases of the study.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Adverse event in ≥2 patients, n (%)</th>
<th>Treatment-emergent events, n (%)</th>
<th>Drug-related treatment-emergent events, n (%)</th>
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<tr>
<td>Oedema peripheral</td>
<td>8 (36.4)</td>
<td>8 (36.4)</td>
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<td>Dyspnoea</td>
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<td>7 (31.8)</td>
<td>6 (27.3)</td>
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<td>Dyspepsia</td>
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<td>5 (22.7)</td>
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<td>Headache</td>
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<td>4 (18.2)</td>
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<td>Feeling hot</td>
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<td>Pancytopenia</td>
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</tr>
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<td>Gastroenteritis</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Hypoxaemia</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Right ventricular failure</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Adverse event in ≥2 patients, n (%)</td>
<td>Treatment-emergent events, n (%)</td>
<td>Drug-related treatment-emergent events, n (%)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total number of patients reporting any event</td>
<td>21 (95.5)</td>
<td>20 (90.9)</td>
<td>15 (68.2)</td>
</tr>
</tbody>
</table>
TABLE 3. Change from baseline in haemodynamic and blood gas parameters following the 12-week treatment and continuation phase of the study. Means ± standard deviation are shown.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th></th>
<th>12 weeks</th>
<th></th>
<th>95% CI</th>
<th></th>
<th>12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Difference (SD)</td>
<td>95% CI</td>
<td>n</td>
<td>Difference (SD)</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>15</td>
<td>4.4 (1.5)</td>
<td>15</td>
<td>+1.2 (1.0)</td>
<td>0.6 to 1.8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>15</td>
<td>2.4 (0.8)</td>
<td>15</td>
<td>+0.7 (0.7)</td>
<td>0.3 to 1.0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn·s·cm⁻⁵</td>
<td>14</td>
<td>648 (207)</td>
<td>14</td>
<td>-120 (93)</td>
<td>-174 to -66</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>Pulmonary artery mean pressure, mmHg</td>
<td>15</td>
<td>40 (10)</td>
<td>15</td>
<td>+1 (10)</td>
<td>-5 to 6</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mmHg</td>
<td>14</td>
<td>7 (5)</td>
<td>14</td>
<td>+1 (5)</td>
<td>-2 to 4</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance,</td>
<td>8</td>
<td>2057 (808)</td>
<td>4</td>
<td>-821 (607)</td>
<td>-1787 to 145</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-----------------------------------</td>
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<td>-----</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>15</td>
<td>79 (14)</td>
<td>+7 (12)</td>
<td>1 to 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>15</td>
<td>65 (6)</td>
<td>+2 (4)</td>
<td>0 to 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO₂, %a</td>
<td>22</td>
<td>94 (3)</td>
<td>-1 (5)</td>
<td>-4 to 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ (capillary), mmHg</td>
<td>19</td>
<td>69 (14)</td>
<td>-7 (12)</td>
<td>-13 to -1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂ (capillary), mmHg</td>
<td>19</td>
<td>38 (7)</td>
<td>-3 (2)</td>
<td>-4 to -2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PaCO₂: arterial partial carbon dioxide pressure; PaO₂: arterial partial oxygen pressure; SaO₂: peripheral oxygen saturation; SD: standard deviation SvO₂: mixed-venous oxygen saturation.

*a measured by pulse oximetry.
FIGURE LEGENDS

FIGURE 1. Study design and patient flow (at 12 month interim analysis)

23 subjects enrolled

1 subject was a screening failure and did not receive study drug

22 subjects received study drug

18 subjects completed 12 weeks of study drug treatment

4 subjects terminated study drug treatment prematurely Reason:
– Adverse events

3 subjects withdrew
Reasons:
– 2 Adverse events
– 1 Withdrawal of consent

15 subjects entered 12-month extension phase

6 subjects terminated study drug treatment prematurely Reasons:
– 2 Adverse events
– 2 Unspecified
– 1 Death
– 1 Lung transplantation

9 subjects completed extension

FIGURE 2. a) cardiac output, b) mean pulmonary artery pressure and c) pulmonary vascular resistance at baseline and after 12 weeks of treatment with riociguat (0.5–2.5 mg t.i.d.). Data are shown for each individual patient, with diagnosis of idiopathic pulmonary fibrosis-associated PH (◆), non-specific interstitial lung disease-associated PH (■), sarcoidosis-associated PH (▲) or scleroderma-associated interstitial lung disease and PH (●) also indicated.
FIGURE 3. Mean change from baseline (± standard deviation) in a) arterial partial carbon dioxide pressure (PaCO₂), b) arterial partial oxygen pressure (PaO₂) and c) peripheral oxygen saturation (SaO₂; measured by pulse oximetry) after treatment with riociguat (0.5–2.5 mg t.i.d).
FIGURE 4. Six-minute walk distance (6MWD) during the 12-week main study and extension study of treatment with riociguat (0.5–2.5 mg t.i.d.). Data are shown for each individual patient, with diagnosis of idiopathic pulmonary fibrosis-associated PH (●), non-specific interstitial lung disease-associated PH (■), sarcoidosis-associated PH (▲) or scleroderma-associated interstitial lung disease and PH (●) also indicated.