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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 $dyn \cdot s \cdot cm^{-5}$ to 528 ± 181 $dyn \cdot s \cdot cm^{-5}$) 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 $dyn \cdot s \cdot cm^{-5}$, 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 (FEV_1) <10% and decrease in diffusing capacity of lung for carbon monoxide (D_LCO) <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 PaO_2 <50 mmHg or a $PaCO_2$ >45 mmHg in room air; other clinically relevant lung diseases including more than mild airflow obstruction (FEV_1/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 (SvO_2) 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 (SaO_2) 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/m^2, 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 ρg/mL at baseline [n=19] vs 1227.6 ± 1352.0 ρg/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_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 to1.8) and cardiac index from 2.4 ± 0.8 L/min/m^2 to 3.0 ± 1.1 L/min/m^2 (difference: +0.7 ± 0.7 L/min/m^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^{-5} to 528 ± 181 dyn·s·cm^{-5} (difference: -120 ± 93 dyn·s·cm^{-5}; 95% CI: -174 to -66) and SVR from 2057 ± 808 dyn·s·cm^{-5} to 1324 ± 278 dyn·s·cm^{-5} (difference: -821 ± 607 dyn·s·cm^{-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_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. PaO_2 decreased by 7 ± 12 mmHg (95% CI: -13 to -1) at 12 weeks and by 3 ± 12 mmHg at 12 months. $PaCO_2$ decreased by 3 ± 2 mmHg (95% CI: -4 to

-2) at 12 weeks and increased by 1 ± 2 mmHg at 12 months (Fig 3). SvO_2 showed a slight improvement between baseline and week 12 (65 ± 6% to 67 ± 7%; difference: +2 ± 4%; 95% CI: 0 to 4).

Pulse oximetry

SaO_2 was measured by pulse oximetry. SaO_2 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 PAP_m was virtually unchanged overall despite the reduction in PVR. In some patients, a flow-mediated increase in PAP_m, 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/m^2) or CTEPH (0.4 (range: 0.2–0.8) L/min/m^2). 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:

1 Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; 31: 1357–1367.

2 Chung F, Dean E. Pathophysiology and cardiorespiratory consequences of interstitial lung disease--review and clinical implications: a special communication. *Phys Ther* 1989; 69: 956–966.

3 Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol* 2009; 54(1 Suppl.): S85–S96.

4 Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J* 2005; 25: 783–788.

5 Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. *Eur Respir J* 2007; 30: 715–721.

6 Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 657–663.

7 Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006; 129: 746–752.

8 Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, Mishima M, Kitaichi M, Izumi T. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; 131: 650–656.

9 Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008; 32: 198–209.

10 Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 891–901.

11 Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008; 31: 407–415.

12 Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 897–899.

13 Foley RJ, Metersky ML. Successful treatment of sarcoidosis-associated pulmonary hypertension with bosentan. *Respiration* 2008; 75: 211–214.

14 Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, Gunther A, Walmrath D, Seeger W, Grimminger F. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet* 2002; 360: 895–900.

15 Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Resp Crit Care Med* 1999; 160: 600–607.

16 Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *New Engl J Med* 2010; 363: 620–628.

17 Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.

18 Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, Hirani N, Hubbard R, Lake F, Millar AB, Wallace WA, Wells AU, Whyte MK, Wilsher ML. Interstitial lung disease guideline: the British Thoracic Society in

collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; 63(Suppl. 5): v1–58.

19 Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations. *Proc Natl Acad Sci U S A* 1977; 74: 3203–3207.

20 Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A* 1987; 84: 9265–9269.

21 McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006; 114: 1417–1431.

22 Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* 2011; 123: 2263–2273.

23 Mittendorf J, Weigand S, Alonso-Alija C, Bischoff E, Feurer A, Gerisch M, Kern A, Knorr A, Lang D, Muenter K, Radtke M, Schirok H, Schlemmer KH, Stahl E, Straub A, Wunder F, Stasch JP. Discovery of riociguat (BAY 63-2521): a potent, oral stimulator of soluble guanylate cyclase for the treatment of pulmonary hypertension. *ChemMedChem* 2009; 4: 853–865.

24 Ghofrani HA, Hoeper MM, Halank M, Meyer FJ, Staehler G, Behr J, Ewert R, Weimann G, Grimminger F. Riociguat for chronic thromboembolic pulmonary

hypertension and pulmonary arterial hypertension: a phase II study. *Eur Respir J* 2010; 36: 792–799.

25 Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, Weissmann N, Muck W, Unger S, Wensing G, Schermuly RT, Ghofrani HA. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. *Eur Respir J* 2009; 33: 785–792.

26 Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E, Smith LJ, Watson KE. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010; 362: 217–227.

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

Variable	**Total study population (n=22)**
Age (years), mean (range)	60.5 (33.0–80.0)
White ethnicity, n (%)	22 (100.0)
Male sex, n (%)	14 (63.6)
BMI (kg/m^2), mean (SD)	26 (4)
WHO functional class	
III, n (%)	19 (86.4)
IV, n (%)	3 (13.6)
6-minute walk distance (m), mean (SD)	316 (96)
Underlying disease	
Idiopathic pulmonary fibrosis, n (%)	13 (59.1)
Non-specific interstitial lung disease, n (%)	5 (22.7)
Sarcoidosis, n (%)	3 (13.6)
Systemic sclerosis, n (%)	1 (4.5)
Pulmonary function	
TLC (% predicted), mean (SD)	67 (12)
FVC (% predicted), mean (SD)	67 (20)
FEV_1 (% predicted), mean (SD)	67 (17)
D_LCO (mmol/min/KPA), mean (SD)*	2.7 (1.5)
Haemodynamics and blood gases	
Mean pulmonary arterial pressure (mmHg), mean (SD)	40 (10)
Pulmonary vascular resistance ($dyn \cdot s \cdot cm^{-5}$), mean (SD)	656 (201)

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)
SaO_2 (%), mean (SD)	94 (3)
SvO_2 (%), mean (SD)†	62 (12)
$PaCO_2$ (mmHg), mean (SD)	39 (7)

BMI: body mass index; D_LCO: diffusing capacity of lung for carbon monoxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $PaCO_2$: arterial partial carbon dioxide pressure; SaO_2: peripheral oxygen saturation; SD: standard deviation; SvO_2: 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.

Adverse events	Adverse event in ≥2 patients, n (%)	Treatment-emergent events, n (%)	Drug-related treatment-emergent events, n (%)
Oedema peripheral	8 (36.4)	8 (36.4)	6 (27.3)
Dyspnoea	7 (31.8)	7 (31.8)	6 (27.3)
Dyspepsia	5 (22.7)	5 (22.7)	3 (13.6)
Nasopharyngitis	5 (22.7)	5 (22.7)	0 (0)
Headache	4 (18.2)	4 (18.2)	3 (13.6)
Feeling hot	3 (13.6)	3 (13.6)	3 (13.6)
Bronchitis	3 (13.6)	3 (13.6)	0 (0)
Pancytopenia	2 (9.1)	2 (9.1)	2 (9.1)
Gastroenteritis	2 (9.1)	2 (9.1)	1 (4.5)
Hypoxaemia	2 (9.1)	2 (9.1)	2 (9.1)
Hypotension	2 (9.1)	2 (9.1)	1 (4.5)
Respiratory failure	2 (9.1)	2 (9.1)	1 (4.5)
Right ventricular failure	2 (9.1)	2 (9.1)	1 (4.5)

Adverse events	Adverse event in ≥2 patients, n (%)	Treatment-emergent events, n (%)	Drug-related treatment-emergent events, n (%)
Respiratory tract infection	2 (9.1)	2 (9.1)	0 (0)
Pulmonary fibrosis	2 (9.1)	1 (4.5)	0 (0)
Diarrhoea	2 (9.1)	2 (9.1)	0 (0)
Total number of patients reporting any event	21 (95.5)	20 (90.9)	15 (68.2)

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.

Parameter	**Baseline**		**12 weeks**			**12 months**	
	n	**Mean (SD)**	**n**	**Difference (SD)**	**95% CI**	**n**	**Difference (SD)**
Cardiac output, L/min	15	4.4 (1.5)	15	+1.2 (1.0)	0.6 to 1.8	-	-
Cardiac index, L/min/m^2	15	2.4 (0.8)	15	+0.7 (0.7)	0.3 to 1.0	-	-
Pulmonary vascular resistance, dyn·s·cm^{-5}	14	648 (207)	14	-120 (93)	-174 to -66	-	-
Pulmonary artery mean pressure, mmHg	15	40 (10)	15	+1 (10)	-5 to 6	-	-
Pulmonary capillary wedge pressure, mmHg	14	7 (5)	14	+1 (5)	-2 to 4	-	-
Systemic vascular resistance,	8	2057 (808)	4	-821 (607)	-1787 to 145	-	-

$dyn \cdot s \cdot cm^{-5}$							
Heart rate, beats per minute	15	79 (14)	15	+7 (12)	1 to 14	-	-
SvO_2, %	15	65 (6)	15	+2 (4)	0 to 4	-	-
SaO_2, %[a]	22	94 (3)	17	-1 (5)	-4 to 1	8	0 (2)
PaO_2 (capillary), mmHg	19	69 (14)	16	-7 (12)	-13 to -1	8	-3 (12)
$PaCO_2$ (capillary), mmHg	19	38 (7)	16	-3 (2)	-4 to -2	8	+1 (2)

$PaCO_2$: arterial partial carbon dioxide pressure; PaO_2: arterial partial oxygen pressure; SaO_2: peripheral oxygen saturation; SD: standard deviation SvO_2: mixed-venous oxygen saturation.

[a]measured by pulse oximetry.

FIGURE LEGENDS

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

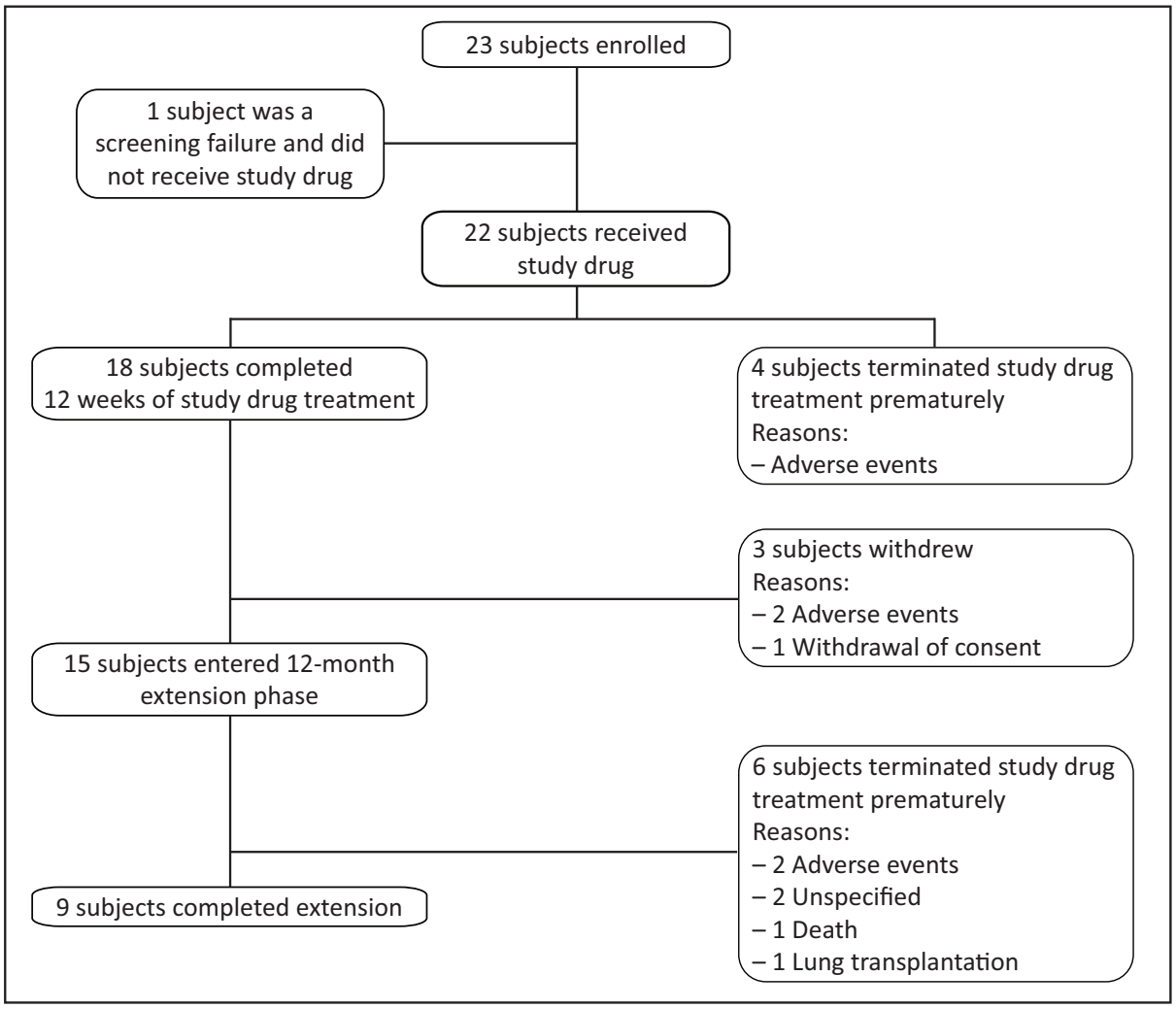


FIGURE 2. a) cardiac output, b) mean pulmonary artery pressure and c) pulmonary vascular resistance at baseline and after 12 weeks of treatment with riociguat (0.5–2.5 mg t.i.d.). Data are shown for each individual patient, with diagnosis of idiopathic pulmonary fibrosis-associated PH (◆), non-specific interstitial lung disease-associated PH (■), sarcoidosis-associated PH (▲) or scleroderma-associated interstitial lung disease and PH (●) also indicated.

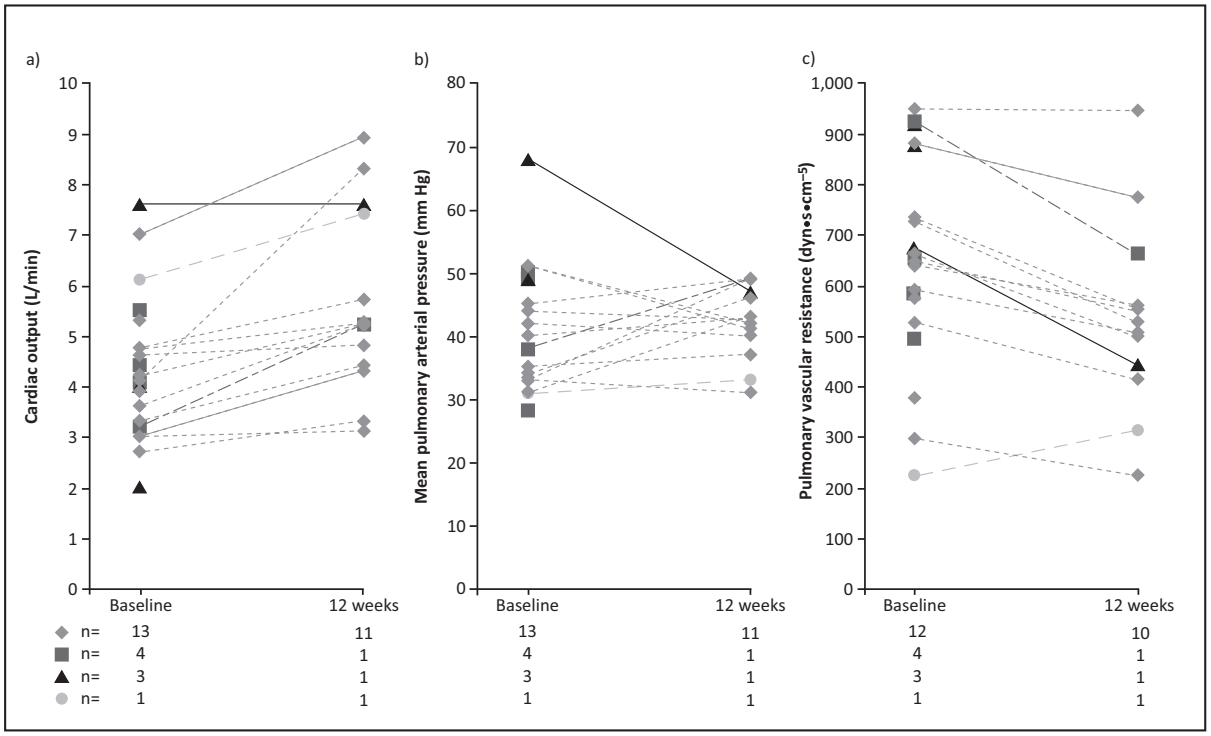


FIGURE 3. Mean change from baseline (± standard deviation) in a) arterial partial carbon dioxide pressure ($PaCO_2$), b) arterial partial oxygen pressure (PaO_2) and c) peripheral oxygen saturation (SaO_2; measured by pulse oximetry) after treatment with riociguat (0.5–2.5 mg t.i.d).

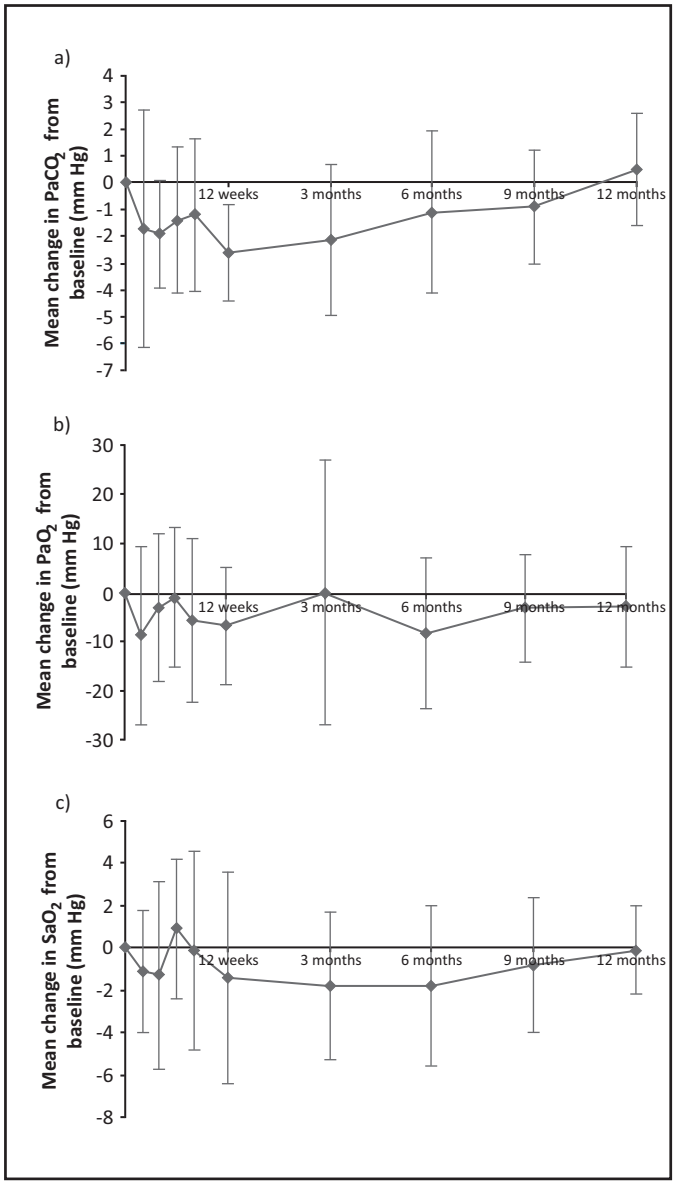
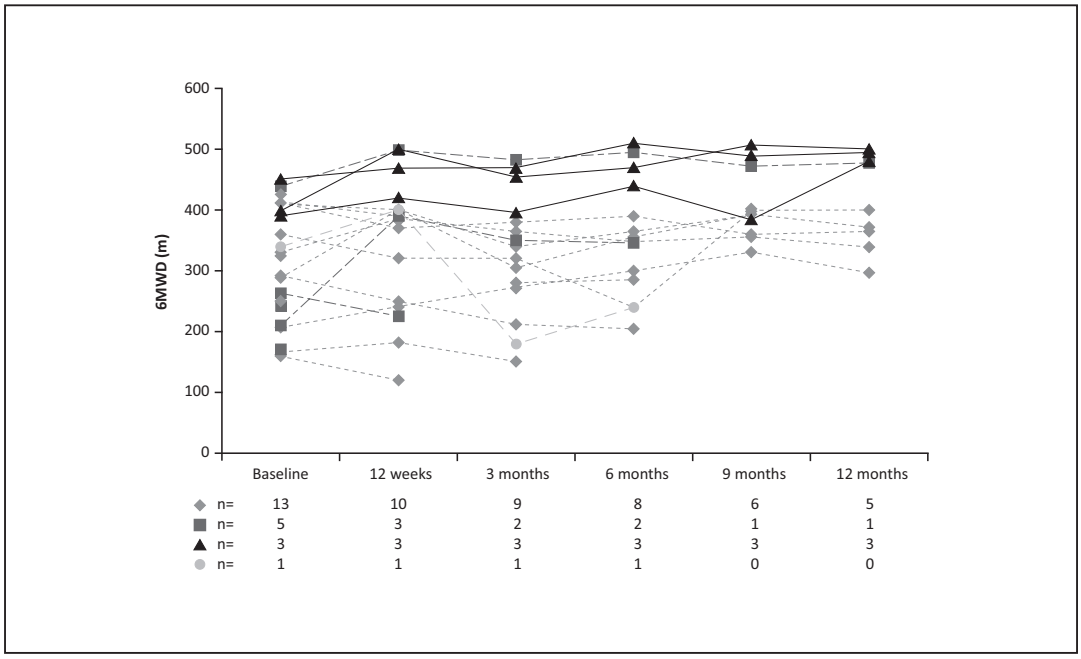


FIGURE 4. Six-minute walk distance (6MWD) during the 12-week main study and extension study of treatment with riociguat (0.5–2.5 mg t.i.d.). Data are shown for each individual patient, with diagnosis of idiopathic pulmonary fibrosis -associated PH (◆), non-specific interstitial lung disease-associated PH (■), sarcoidosis-associated PH (▲) or scleroderma-associated interstitial lung disease and PH (●) also indicated.


600
500
400
300
200
100
0
6MWD (m)
Baseline
12 weeks
3 months
6 months
9 months
12 months
n= 13 10 9 8 6 5
n= 5 3 2 2 1 1
n= 3 3 3 3 3 3
n= 1 1 1 1 0 0