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# First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension

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**ABSTRACT:** **Pulmonary hypertension (PH) is associated with impaired production of the vasodilator nitric oxide (NO). Riociguat (BAY 63-2521; Bayer Healthcare AG, Wuppertal, Germany) acts directly on soluble guanylate cyclase, stimulating the enzyme and increasing sensitivity to low NO levels. The present study evaluates riociguat safety, tolerability and efficacy in patients with moderate-to-severe PH (pulmonary arterial hypertension, distal chronic thromboembolic PH or PH with mild to moderate interstitial lung disease).**

**The optimal tolerated dose was identified by incremental dosing in four patients with PH; pharmacodynamic and pharmacokinetic parameters were assessed following single-dose administration (2.5 mg or 1 mg) in 10 and five patients with PH, respectively. All subjects (n=19) were analysed for safety and tolerability.**

**Riociguat had a favourable safety profile at single doses $\leqslant$2.5 mg. It significantly improved pulmonary haemodynamic parameters and cardiac index in patients with PH in a dose-dependent manner, to a greater extent than inhaled NO. Although riociguat also had significant systemic effects and showed no pulmonary selectivity, mean systolic blood pressure remained $>$110 mmHg.**

**The present report is the first to describe the use of riociguat in patients with pulmonary hypertension. The drug was well-tolerated and superior to nitric oxide in efficacy and duration. Riociguat, therefore, has potential as a novel therapy for pulmonary hypertension and warrants further investigation.**

**KEYWORDS:** **Maximum tolerated dose, pharmacokinetics, phase-II clinical trial, pulmonary hypertension, soluble guanylyl cyclase, vasodilation**

Pulmonary arterial hypertension (PAH) defines a group of conditions characterised by increased pulmonary vascular resistance (PVR) leading to reduced right heart function and eventual heart failure [1]. It is a progressive disease with an extremely poor prognosis; if left untreated, median life expectancy following diagnosis is 2.8 yrs [2]. Although rare in the general population (15–52 cases per million) [3, 4], its prevalence increases in association with certain conditions. For example, PAH is diagnosed in ~0.5% of patients infected with HIV [5], 8–29% of patients with scleroderma [6, 7] and 11–32% of patients with sickle cell disease [8, 9].

PAH is caused by pulmonary vasoconstriction with vascular remodelling, formation of plexiform lesions and *in situ* thrombosis, which occur in response to aberrant production of a number of signalling factors. Expression of the vasoconstrictor endothelin is increased, while production of vasodilators such as prostacyclin and nitric oxide (NO) is decreased [10]. In healthy individuals, endothelial cell-derived NO acts on smooth muscle cells to induce vasodilation by increasing production of the second messenger cyclic guanosine monophosphate (cGMP) *via* activation of soluble guanylate cyclase (sGC) [11, 12].

Recent years have seen substantial progress in the treatment of PAH, with the development of palliative therapies that target the NO, endothelin and prostacyclin signalling pathways to promote vasodilation. However, although these

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developments have improved outcomes for patients with PAH, survival rates and quality of life remain relatively low [13].

Treatment of pulmonary hypertension (PH) with NO-releasing agents such as nitrates has failed to produce beneficial long-term effects as, in most cases, negligible pulmonary vasodilatation was counterbalanced by significant peripheral reduction in vascular resistance and reflex tachycardia [14], which are poorly tolerated by patients with severe PH. Inhaled NO is widely used as a short-term vasodilator to identify so-called responders to calcium channel blockers [15]. The long-term use of NO, however, is hampered by technical problems of administration, and life-threatening rebound PH can occur following interruption or discontinuation of NO inhalation [14]. An alternative therapeutic strategy targets downstream components of the NO signalling pathway by inhibiting phosphodiesterase-5, which regulates the conversion of the second messenger cGMP to GMP [16]. Sildenafil has been the lead substance in this group of agents, showing both acute and long-term beneficial effects in patients with PAH [17, 18]. However, phosphodiesterase-5 inhibition is not effective in all patients with PH [19]. The full therapeutic potential of the NO signalling pathway, therefore, remains to be exploited.

Riociguat (BAY 63-2521; Bayer Healthcare AG, Wuppertal, Germany) offers a new mode of action for the treatment of PAH: in preclinical studies, it has been shown to stimulate sGC directly, increasing the enzyme's activity independently of NO, while also increasing sensitivity to low levels of NO. Treatment of two rodent models of PH with riociguat reduced pulmonary arterial pressure (PAP) and partially reversed cardiac hypertrophy and vascular remodelling [20]. The aim of the present clinical study was to evaluate the short-term safety profile, tolerability and efficacy of riociguat in patients with moderate to severe PH.

## METHODS

### *Patients*

Male and female patients aged 18–80 yrs were eligible for inclusion if they had a mean PVR >300 dyn·s·cm$^{-5}$ and a diagnosis of PAH, distal chronic thromboembolic PH or PH associated with mild to moderate interstitial lung disease. Catheters for haemodynamic measurements were placed on clinical grounds independently of the trial. A 12-h washout period was observed for acute vasodilatory substances such as calcium channel blockers and phosphodiesterase-5 inhibitors.

Patients were excluded from the study if they had any of the following: pre-existing lung diseases (other than interstitial lung disease as defined in the protocol), significant left heart dysfunction, significantly impaired gas exchange (partial pressure of carbon dioxide in arterial blood ($P_{a,CO_2}$) >55 mmHg (>7.3 kPa)), deficiencies of blood coagulation or evidence of latent bleeding risk, sickle cell anaemia, peripheral organ dysfunction or immunodeficiencies. Females with child-bearing potential were excluded if they were not using a

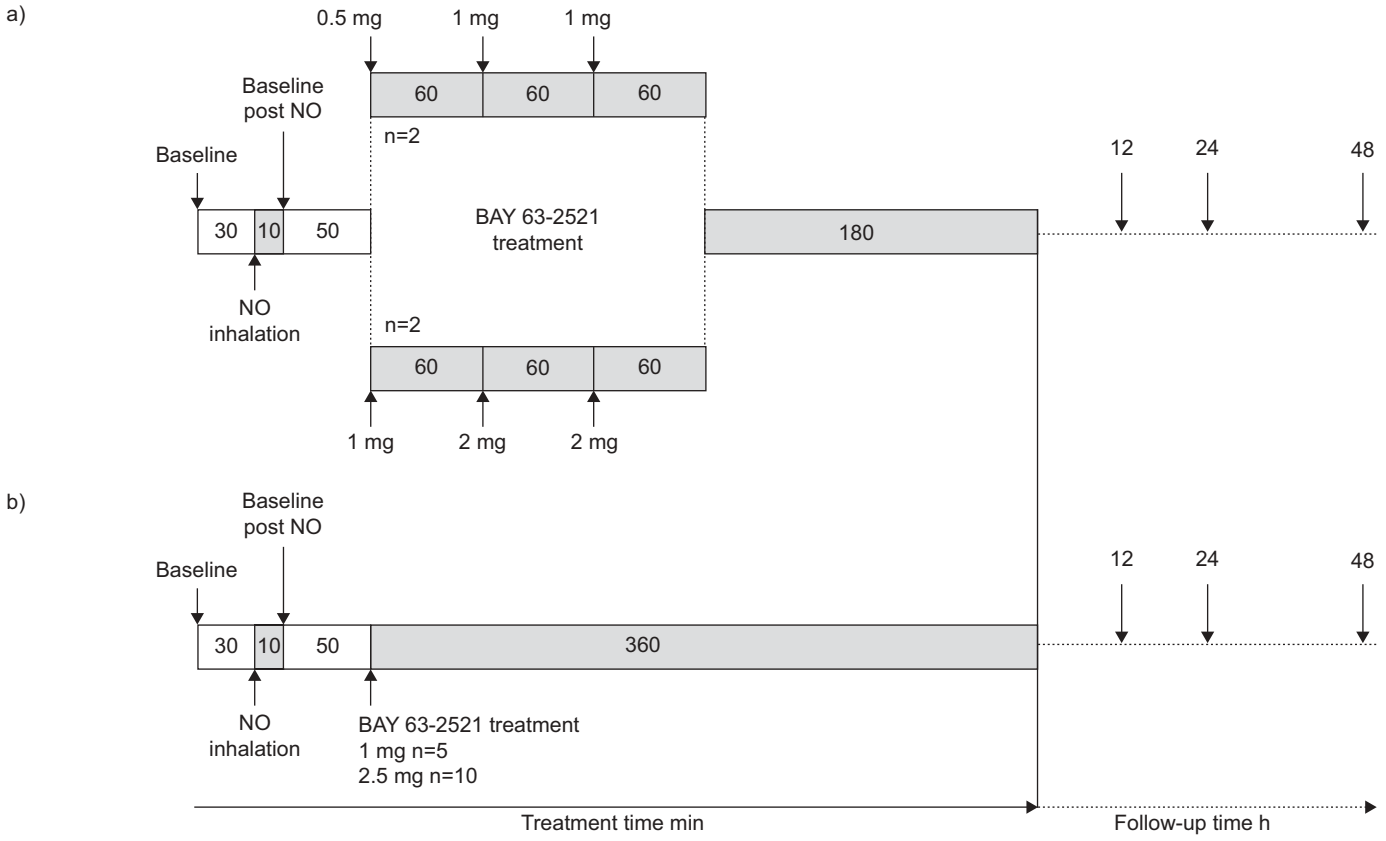


**FIGURE 1.** Treatment schedules for evaluation of riociguat (BAY 63-2521) in patients with pulmonary hypertension. a) Identification of maximum tolerated dose. b) Evaluation of 1 mg and 2.5 mg doses. NO: nitric oxide.

**TABLE 1** Treatment-emergent adverse events and possible relationship to study drug

| | iNO | Riociguat | | | |
|---|---|---|---|---|---|
| | | Incremental dose | | Single dose | |
| | | 0.5+1+1 mg | 1+2+2 mg | 1 mg | 2.5 mg |
| **Subjects n** | 19 | 2 | 2 | 5 | 10 |
| **Adverse events#** | 0 (0) | 1 (50) | 1 (50) | 1 (20) | 1 (10) |
| **Renal and urinary disorders** | | Micturition urgency¶ | Urinary retention¶ | | |
| **Vascular disorders** | | Hot flush+ | | | |
| **Nervous system disorders** | | | | Dizziness+ | |
| **Respiratory, thoracic and mediastinal disorders** | | | | Cough¶ | Nasal congestion+ |

Data are presented as n (%), unless otherwise stated. iNO: inhaled nitric oxide. #: all adverse events were mild in severity; ¶: not drug related; +: at least possibly drug related.

reliable contraceptive measure. Patients were also excluded if they had participated in another study during the 30 days preceding the current study, or if they had undergone previous therapeutic radiation of lung or mediastinum. During the trial, use of medication other than the investigational product was permitted only after consultation with the investigator, and all concomitant medications were documented.

### *Study design*

Riociguat was administered in the morning after a fasting period of $\geqslant$8 h. After a first baseline evaluation lasting 30 min, every patient underwent a NO inhalation period of 10 min (10–20 ppm NO required for maximum vasodilatation), followed by a second baseline period of 50 min. Haemodynamic and gas exchange variables were measured twice during the NO inhalation period and the second baseline period. BAY 63-2521 was administered orally in solution (unit of dosage: 0.5 mg·mL$^{-1}$) after haemodynamic variables returned to baseline values.

In part A of the study, which was designed to identify the dose of riociguat that has maximal clinical effect without compromising safety and tolerability, four patients were given hourly incremental doses (0.5+1+1 mg=2.5 mg (n=2) and 1+2+2 mg=5 mg (n=2)). Dose titration was terminated if the mean arterial pressure fell to <60 mmHg or if the heart rate exceeded 140 beats·min$^{-1}$ (fig. 1a). In part B, 1 mg and 2.5 mg single doses of riociguat were evaluated in five and 10 patients, respectively (fig. 1b). Measurements obtained for riociguat treatment were compared with peak intervention values for inhaled NO and post-NO intervention baseline values.

The study protocol and any substantial amendments were approved by the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; Bonn, Germany) and the Ethics Committee of the University of Giessen Medical Faculty (Giessen, Germany). Each patient gave written informed consent.

**TABLE 2** Baseline pharmacodynamic characteristics in study part B

| Parameter | Riociguat | |
|---|---|---|
| | 1 mg | 2.5 mg |
| **Subjects n** | 5 | 10 |
| **mPAP mmHg** | 55.4±16.6 | 42.1±11.3 |
| **PVR dyn·s·cm$^{-5}$** | 1028±491 | 566±209 |
| **SBP mmHg** | 147±25 | 133±20 |
| **SVR dyn·s·cm$^{-5}$** | 2127±407 | 1324±335 |
| **Cardiac index L·min$^{-1}$·m$^{-2}$** | 2.17±0.18 | 2.74±0.82 |
| **Heart rate beats·min$^{-1}$** | 84±12 | 73±10 |

mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; SBP: systolic blood pressure; SVR: systemic vascular resistance.

### *Safety and tolerability*

Safety and tolerability were evaluated using standard vital sign and laboratory biochemistry. The subjective tolerability of riociguat was evaluated by questioning the subjects about adverse events or by spontaneous reporting of adverse events. Clinical adverse events were classified according to their degree of severity (mild, moderate or severe), and it was also noted whether or not they were serious. Patients were assessed for 48 h following administration of riociguat.

### *Pharmacodynamics*

The pharmacodynamic effects of the drug were assessed using Swan-Ganz catheterisation, blood gas measurements and multiple inert gas elimination technique (MIGET) as described previously [21].

Swan-Ganz haemodynamic measurements included direct measurements, such as mean right atrial pressure (mRAP; mmHg), pulmonary arterial pressures (systolic PAP, diastolic PAP and mean PAP (mPAP; mmHg)), pulmonary capillary wedge pressure (PCWP; mmHg), heart rate (beats·min$^{-1}$), systemic blood pressure (systolic (SBP), diastolic and arterial mean (mSAP); mmHg), cardiac output (CO; L·min$^{-1}$ (average of three measurements, performed and calculated by CO thermodilution device)), body weight (kg) and height (cm).

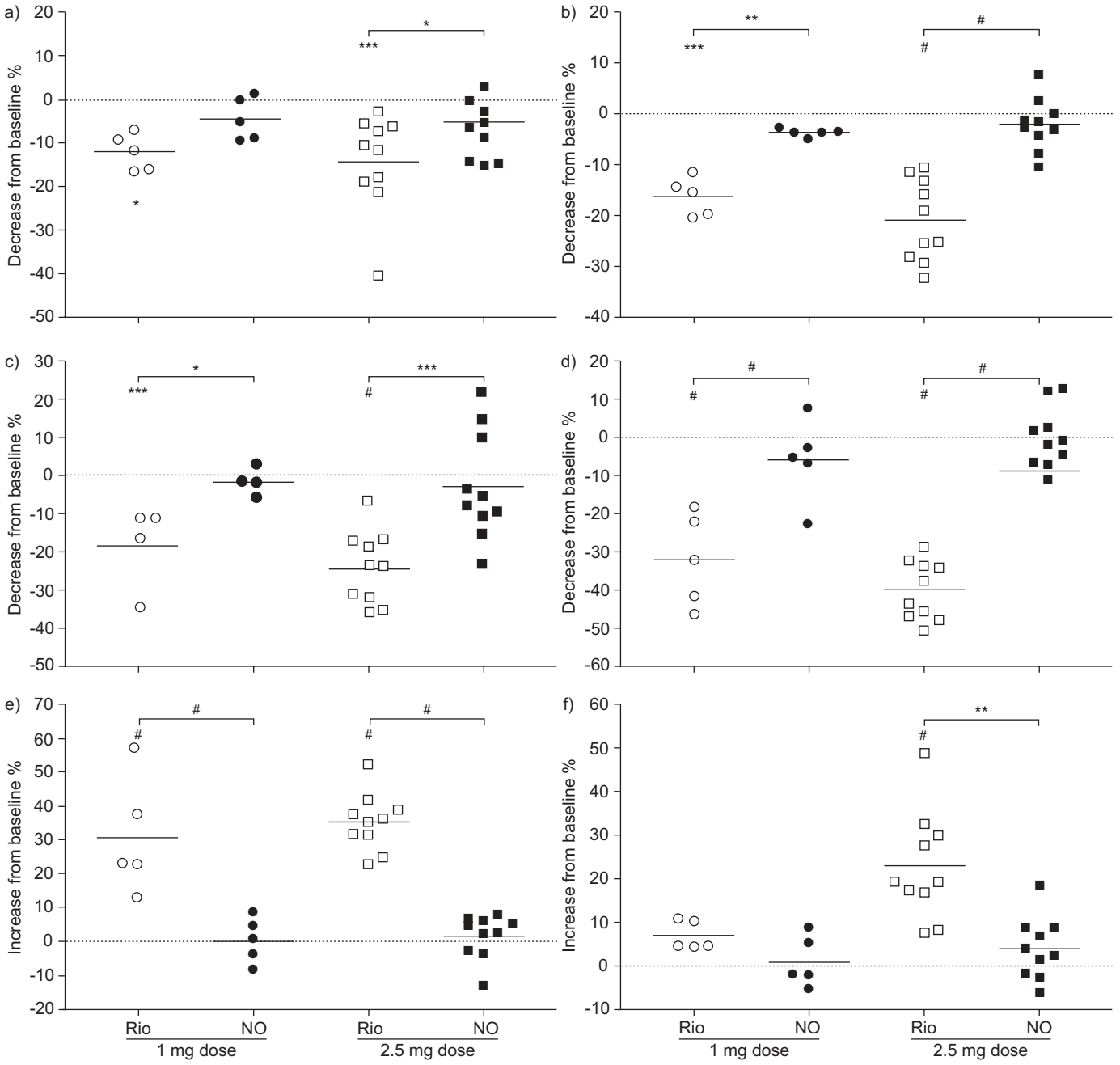


**FIGURE 2.** Changes in haemodynamic parameters following a single dose of riociguat (Rio) compared with inhaled nitric oxide (NO). Percentage decrease from baseline of a) mean pulmonary arterial pressure, b) systolic blood pressure, c) pulmonary vascular resistance and d) systemic vascular resistance. Percentage increase from baseline of e) cardiac index and f) heart rate. Horizontal lines indicate point estimates (least-squares means) in each case. Statistical significance was measured by the F statistic. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; #: $p<0.0001$.

Calculated measurements included body surface area (BSA; equation 1, Dubois formula), PVR (equation 2), systemic vascular resistance (SVR; equation 3) and cardiac index (equation 4).

$$\text{BSA (in m}^2\text{)} = \text{weight (in kg)}^{0.425} \times \text{height (in cm)}^{0.725} \times 0.007184 \quad (1)$$

$$\text{PVR (in dyn·s·cm}^{-5}\text{)} = 80 \times (\text{PAP-PCWP})/\text{CO} \quad (2)$$

$$\text{SVR (in dyn·s·cm}^{-5}\text{)} = 80 \times (\text{mSAP-mRAP})/\text{CO} \quad (3)$$

$$\text{cardiac index (in L·min}^{-1}\text{·m}^{-2}\text{)} = \text{CO/BSA} \quad (4)$$

Blood gas analysis measurements included arterial oxygen tension ($P_{a,O_2}$; mmHg), $P_{a,CO_2}$ (mmHg), arterial oxygen saturation (%), mixed venous oxygen tension (mmHg) and venous oxygen saturation (%).

MIGET measured total ventilation (L·min$^{-1}$), total perfusion (L·min$^{-1}$), deadspace ventilation (per cent of total ventilation), low ventilation/perfusion ($V'/Q'$) perfusion ($V'/Q'$ 0.001–0.1%

of total perfusion), normal $V'/Q'$ perfusion ($V'/Q'$ 0.1–10% of total perfusion), ventilation–perfusion distribution (standard deviation of perfusion and standard deviation of ventilation) and intrapulmonary shunt flow (per cent of total perfusion).

In order to assess the relationship between riociguat plasma concentration and the effect on PAP, SBP, PVR, SVR and cardiac index (measured as the ratio to baseline), Spearman's rank correlation coefficients along with 95% confidence intervals were calculated for each parameter and all subjects.

### Pharmacokinetics

Riociguat plasma concentrations were determined by HPLC–MS assay, using blood samples obtained at regular intervals up to 48 h after riociguat administration. Primary parameters included the following: area under the plasma concentration *versus* time curve from zero to infinity (AUC); AUC divided by dose (mg), expressed per kg body weight ($AUC_{norm}$); maximum drug concentration in plasma after single dose administration ($C_{max}$); and $C_{max}$ divided by dose (mg), expressed per kg body weight ($C_{max,norm}$). Secondary parameters included time to reach maximum drug concentration in plasma, and half-life associated with terminal elimination. Apparent volume of distribution during terminal phase after oral administration and total body clearance of drug from plasma after oral administration were also calculated.

The influence of riociguat dose on pharmacokinetic parameters was assessed by performing an explorative ANOVA (including factor ''dose'') on the log-transformed values of $AUC_{norm}$ and $C_{max,norm}$ in the single-dose study.

## RESULTS

### Patient demographics

Patient demographics are summarised in the online supplementary material. There was no clinically relevant difference in patient demographics between study part A and part B. Patients enrolled in part B showed no statistically significant differences in age, height, weight or body mass index between dose groups. The 1 mg dose group had a higher proportion of females than the 2.5 mg dose group. Medications used by patients prior to the study are presented in the online supplementary material.

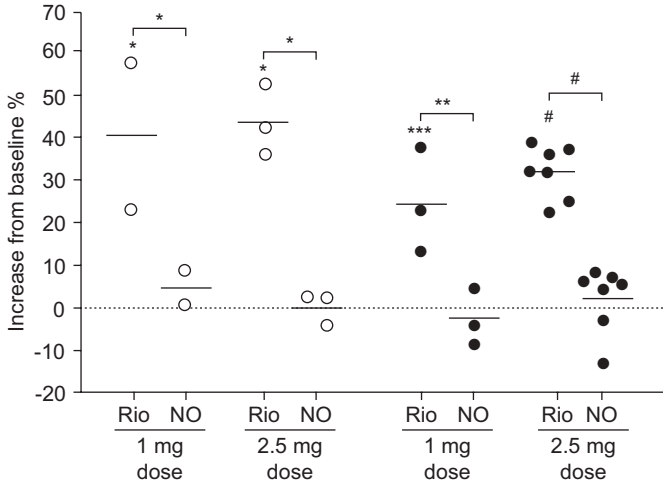


**FIGURE 3.** Change from baseline of cardiac index in patients with distal chronic thromboembolic pulmonary hypertension (○) or pulmonary arterial hypertension (●) following a single dose of riociguat (Rio) compared with inhaled nitric oxide (NO). Horizontal lines indicate point estimates (least-squares means) in each case. Statistical significance was measured by the F statistic. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; #: $p<0.0001$. No significant differences in response to drug were observed between the two disease entities.

### Safety and tolerability

No serious adverse events occurred in the study (table 1). Overall, six mild adverse events were documented in four out of 19 patients, all of which had resolved by study completion. Three adverse events were considered to be drug-related and attributable to the pharmacological properties of the test compound.

Riociguat at a dose of $\leqslant$2.5 mg had no clinically relevant effects on vital signs, electrocardiograms or laboratory values, and no major changes were noted in blood gases ($Pa,O_2$, $Pa,CO_2$, blood oxygen saturation) or $V'/Q'$ matching. Riociguat was well tolerated up to 2.5 mg, whereas a total dose of 5 mg in study part A caused asymptomatic hypotension in one patient. Therefore, a 2.5 mg dose was used in part B to demonstrate efficacy; 1 mg was chosen to test for the first effect level.

### Pharmacodynamics

Baseline pharmacodynamic parameters are shown in table 2. Inhaled NO led to small, nonsignificant reductions from baseline in mPAP, SBP, PVR and SVR, and no relevant changes were observed for cardiac index or heart rate (fig. 2). mPAP, SBP, PVR and SVR showed a similar maximum decrease in response to NO inhalation in both 1 mg and 2.5 mg dose groups.

Both 1 and 2.5 mg doses of riociguat caused clinically relevant and statistically significant reductions from baseline in mPAP, PVR, SBP and SVR to a similar extent. A clinically relevant and statistically significant increase in cardiac index was also observed with both doses (p-value between 0.0151 and $<0.0001$; fig. 2), whereas a significant increase in heart rate was only observed in the 2.5 mg dose group. Both doses of riociguat were superior to NO in reducing PVR, SBP and SVR and increasing cardiac index (p-value between 0.0220 and $<0.0001$; fig. 2), and the 2.5 mg dose was superior to NO in reducing mPAP ($p=0.0341$; fig. 2a). Riociguat had a similar effect in patient subgroups with PAH or chronic thromboembolic PH, significantly increasing cardiac index to a greater extent than NO (fig. 3). Riociguat plasma concentrations correlated significantly with the reductions in mPAP, SBP, PVR and SVR, and the concomitant increase in cardiac index (table 3; fig. 4a). Neither dose of riociguat produced any deterioration in gas exchange or $V'/Q'$ matching (as measured by MIGET), despite causing strong pulmonary vasodilation (see online supplementary material).

### Pharmacokinetics

Following single-dose administration of riociguat solution, plasma concentrations of riociguat showed dose-dependent increases with pronounced interindividual variability (fig. 4b). Peak concentrations of riociguat were reached after 0.25–1.5 h, and its half-life was 10–12 h (table 4). $C_{max}$ and AUC values for riociguat suggested dose proportionality for the 1 and 2.5 mg

**TABLE 3** Statistics on Spearman correlation between riociguat drug concentration and pulmonary arterial pressure (PAP), systolic blood pressure (SBP), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) and cardiac index

| Parameter | Unit | Correlation (95% CI) | Two-sided p>\|Z\| |
|---|---|---|---|
| **PAP** | mmHg | -0.2550 (-0.3827– -0.1274) | <0.0001 |
| **SBP** | mmHg | -0.5569 (-0.6531– -0.4607) | <0.0001 |
| **PVR** | dyn·s·cm$^{-5}$ | -0.4733 (-0.5815– -0.3650) | <0.0001 |
| **SVR** | dyn·s·cm$^{-5}$ | -0.5910 (-0.6879– -0.4942) | <0.0001 |
| **Cardiac index** | L·min$^{-1}$·m$^{-2}$ | 0.4543 (0.3411–0.5674) | <0.0001 |

Subjects valid for pharmacokinetic and pharmacodynamic analysis; n=19. CI: confidence interval.

doses (table 4); this was supported by ANOVA results, which showed that factor dose had no influence on either parameter ($AUC_{norm}$, p=0.7559; $C_{max,norm}$, p=0.6128).

## DISCUSSION

In the present proof-of-concept study in patients with PAH, distal chronic thromboembolic PH or PH associated with mild to moderate interstitial lung disease (mean PVR >300 dyn·s·cm$^{-5}$), doses of 1 or 2.5 mg of riociguat significantly reduced PVR and also improved PAP and cardiac index in a concentration-dependent manner. Both doses demonstrated greater potency and duration of action than inhaled NO, which had a small, statistically insignificant effect in the study, consistent with the fact that a substantial proportion of PH patients does not respond to NO inhalation [22]. Neither dose of riociguat produced any deterioration in gas exchange or $V'/Q'$ matching, despite strong pulmonary vasodilation.

Riociguat had a favourable safety profile, with a single dose of 2.5 mg being well tolerated. A total dose of 5 mg administered in hourly increments gave rise to asymptomatic hypotension in one patient in part A; therefore, subsequent tests were limited to a maximum dose of 2.5 mg. The favourable safety profile observed in the present study is in agreement with a previous phase-I study, in which riociguat at oral doses of up to 5.0 mg was well tolerated by healthy male volunteers [23].

Oral riociguat was effective in the current study, thus offering the patient a simple and convenient mode of administration. Oral therapies currently approved for the treatment of PAH comprise endothelin receptor agonists (ERAs) and phosphodiesterase-5 inhibitors. Although these therapies have helped to improve the prognosis for patients with PAH, survival rates remain relatively poor [13], suggesting that a new approach is required. In addition, ERAs are associated with an increased risk of hepatotoxicity [24]. Riociguat did not demonstrate any hepatotoxicity in the current short-term study, supporting previous work in experimental models and human volunteer studies [23]: no significant abnormalities in laboratory values were recorded in association with the trial, apart from one case of slightly elevated glutamate dehydrogenase, pre-existent in a patient who had been treated with

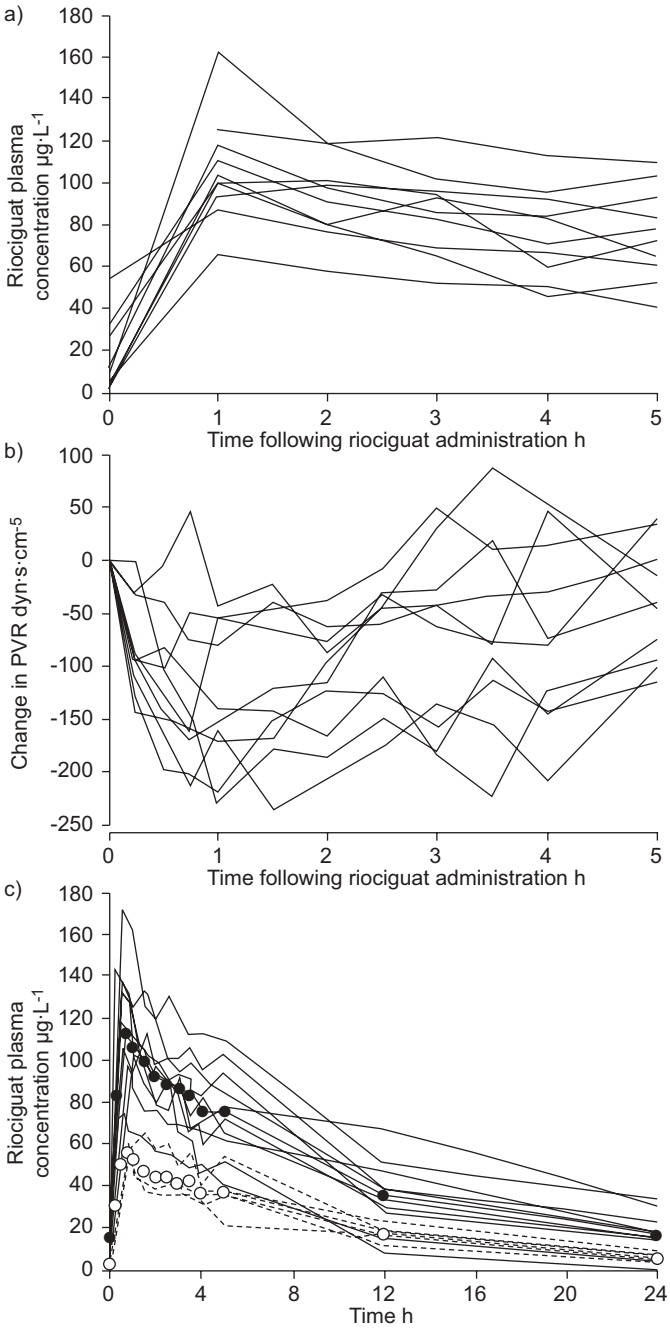


**FIGURE 4.** Pharmacokinetic analysis of riociguat following a single oral dose. Comparison of a) riociguat plasma concentration with b) changes in pulmonary vascular resistance (PVR) from baseline over time. c) Study part B: riociguat plasma concentrations following a single oral dose of 1 mg and 2.5 mg riociguat solution. Data are shown for each individual patient, and geometric means for the 2.5 mg (●) and 1 mg (○) dose groups are also indicated. Subjects valid for pharmacokinetic analysis; n=15.

ERAs before the study and who had a history of intermittent increases of liver enzymes.

The phosphodiesterase-5 inhibitor sildenafil is widely used and well-tolerated as a therapy for PAH, and has demonstrated a degree of pulmonary selectivity despite being administered orally [25], presumably due to the relatively

**TABLE 4** Study part B: pharmacokinetic parameters of riociguat in plasma following single-dose administration of 2.5 and 1 mg riociguat

| Parameter | Riociguat 1 mg | | | Riociguat 2.5 mg | | |
|---|---|---|---|---|---|---|
| | Geometric mean | CV % | Range | Geometric mean | CV % | Range |
| AUC $\mu g \cdot h \cdot L^{-1}$ | 602.3 | 14.9 | 456.5–749.6 | 1411 | 39.2 | 597.5–3121 |
| $C_{max}$ $\mu g \cdot L^{-1}$ | 59.43 | 5.9 | 53.49–65.05 | 119.4 | 16.1 | 74.69–172.4 |
| $t_{max}$ h | 0.750# | | 0.500–1.500 | 0.500# | | 0.250–1.500 |
| $t_{1/2}$ h | 9.953 | 8.6 | 8.737–12.14 | 11.65 | 38.6 | 4.680–28.58 |
| Vz/f $L \cdot kg^{-1}$ | 0.354 | 7.3 | 0.307–0.393 | 0.378 | 20.7 | 0.005–0.609 |
| CL/f $L \cdot h^{-1}$ | 1.660 | 14.9 | 1.334–2.191 | 1.771 | 39.2 | 0.801–4.184 |

Subjects valid for pharmacokinetic and pharmacodynamic analysis; n=15 (n=5 in 1 mg dose group and n=10 in 2.5 mg dose group). CV: coefficient of variance (geometric); AUC: area under plasma concentration/time curve from zero to infinity after single dose; $C_{max}$: maximum drug concentration in plasma after single-dose administration; $t_{max}$: time to reach maximum drug concentration in plasma; $t_{1/2}$: terminal elimination half-life; Vz/f: apparent volume of distribution during terminal phase after oral administration; CL/f: total body clearance of drug from plasma calculated after oral administration. #: median.

high expression of phosphodiesterase-5 in the lung [26]. However, its efficacy is dependent on the presence of an intact NO-sGC-cGMP axis [27], and may be limited in the presence of low levels of NO; sildenafil blocks degradation of cGMP and, thus, depends on the presence of NO stimulating sGC, in contrast to riociguat which can increase cGMP synthesis in the absence of NO. Although various doses of sildenafil (20–80 mg *t.i.d.*) were used in the SUPER-1 (sildenafil use in pulmonary arterial hypertension) trial [18], and the bulk of long-term experience with this drug is with doses of >20 mg *t.i.d.*, agencies have only approved the lowest dose of 20 mg *t.i.d.* for long-term treatment, which could be too low for some patients [16]. The synergistic action of riociguat with low levels of NO may provide a means to increase cGMP levels and, thus, promote vasodilation in combination with sildenafil or in patients who do not respond to sildenafil, while also ensuring maintenance of $V'/Q'$ matching.

Riociguat significantly reduced SBP and SVR in the current study and, therefore, did not demonstrate pulmonary selectivity although, interestingly, the systemic vasodilation was not accompanied by any relevant side-effects (table 1). This may have been due to a compensatory increase in CO. Although the observed systemic effects of riociguat were asymptomatic in the present short-term study of supine patients, its long-term effect on mobile patients may be more significant and must be examined in future studies.

The current study has certain limitations, for example the small and heterogeneous patient population exposed to the drug, lack of a placebo group and the observation of short-term effects only. In addition, plasma cGMP levels, which would have provided information regarding the direct effect of riociguat on sGC activity, were not assessed. Nevertheless, the results of the study present riociguat as a promising novel therapeutic principle that warrants further investigation.

Direct NO-independent stimulation of sGC and sensitisation of sGC to low levels of endogenous NO may offer distinct advantages over current therapeutic approaches and opens access to a completely new class of drugs for cardiovascular indications [28]. Riociguat stimulates the NO target sGC directly to create a strong vasodilatory effect irrespective of integrity of endothelial function and NO production, and also acts synergistically in the presence of NO, offering a new mode of action for the treatment of PH. In the present study, convenient oral doses of riociguat demonstrated efficacy, tolerability and durable action, with no deterioration in gas exchange. Comparison of this promising drug with established therapies, such as sildenafil, and assessment of its efficacy as an add-on therapy or in patients who do not respond to existing treatments, would be of great interest in future studies.

In conclusion, the present study demonstrates the efficacy of riociguat in lowering pulmonary vascular resistance and improving cardiac function in patients with moderate-to-severe pulmonary hypertension. Therefore, as a representative of a new class of drugs hitherto not evaluated in cardiovascular disease, riociguat offers great therapeutic potential as a treatment for patients with pulmonary vascular disorders. The encouraging results of the current acute haemodynamic study warrant further long-term controlled clinical trials in this field. A multicentre phase-II trial has recently been initiated to address this issue.

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