Acute effects of riociguat in borderline or manifest pulmonary hypertension associated with chronic obstructive pulmonary disease

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Abstract: Riociguat is the first oral soluble guanylate cyclase stimulator shown to improve pulmonary hemodynamics in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (PH). This pilot study assessed the impact of a single dose of riociguat on hemodynamics, gas exchange, and lung function in patients with PH associated with chronic obstructive pulmonary disease (COPD). Adults with COPD-associated borderline or manifest PH (pulmonary vascular resistance > 270 dyn·s·cm^{-5}, mean pulmonary artery pressure ≥ 23 mmHg, ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity < 70%, and partial pressure of oxygen and carbon dioxide in arterial blood > 50 and ≤ 55 mmHg, respectively) received riociguat 1 or 2.5 mg during right heart catheterization. Twenty-two patients completed the study (11 men, 11 women, aged 56–82 years; 1-mg group: n = 10 [mean FEV_1: 43.1%]; 2.5-mg group: n = 12 [mean FEV_1: 41.2%]). Riociguat caused significant improvements (P < 0.01) from baseline in mean pulmonary artery pressure (1 mg: −3.60 mmHg [−11.44%]; 2.5 mg: −4.83 mmHg [−14.76%]) and pulmonary vascular resistance (1 mg: −58.32 dyn·s·cm^{-5} [−15.35%]; 2.5 mg: −123.8 dyn·s·cm^{-5} [−32.96%]). No relevant changes in lung function or gas exchange were observed. Single doses of riociguat were well tolerated and showed promising hemodynamic effects without untoward effects on gas exchange or lung function in patients with COPD-associated PH. Placebo-controlled studies of chronic treatment with riociguat are warranted.

Keywords: clinical trial, hemodynamics, multiple inert-gas elimination technique, pulmonary gas exchange, soluble guanylate cyclase.

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Pulmonary hypertension (PH) is a progressive and debilitating condition associated with a sustained increase in pulmonary artery pressure (PAP) that results from excessive vasoconstriction and remodeling of the pulmonary arteries.[1,2] In chronic obstructive pulmonary disease (COPD), estimates of the prevalence of associated PH are wide ranging (30%–70%), depending on the PH definition used.[3-6] In about 20% of patients, COPD is associated with "borderline PH," defined as a mean PAP between 21 and 24 mmHg. Mean PAP in healthy individuals has been reported to be 14 ± 3 mmHg at rest, with the upper limit of normal being defined as 20 mmHg.[7,8] It has been suggested previously that a mean PAP greater than 20 mmHg is associated with morbidity and mortality.[5] Thus, pulmonary vascular changes may be present even in borderline PH. Increased PAP is thought to be induced by hypoxic and inflammatory triggers leading to intimal proliferation in mild COPD,[9] and by loss of lung tissue and small pulmonary vessels in emphysema. Recent data suggest that pulmonary vascular changes may precede the onset of airway and parenchymal disease associated with tobacco smoke exposure.[10] Furthermore, COPD-associated PH may be induced by left ventricular diastolic dysfunction in some patients. Although long-term oxygen therapy improves survival in patients with COPD,[3] the prognosis for patients with COPD and mean PAP greater than 25 mmHg remains poor.[11-13]

A balance of vasodilation and vasoconstriction is maintained in the healthy lung by vasodilatory agents such as nitric oxide (NO) and prostacyclins and by vasoconstrictive agents such as thromboxane A_2 and endothelin.[14] In PH, this balance is compromised because of the reduced bioavailability of NO and prostacyclins and increased production of endothelin.[15] NO promotes vasodilation by

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stimulating soluble guanylate cyclase (sGC), which increases production of the secondary messenger cyclic guanosine monophosphate.[14,16] Analyses of pulmonary arterial smooth muscle cells from patients with PH and animal models of PH have demonstrated upregulation of sGC.[17] While this upregulation does not appear to compensate for the low level of endogenous NO in PH, it demonstrates that sGC could be a potential target for treatment. In support of this, sGC stimulation reversed right heart hypertrophy and lung vascular remodeling in preclinical studies.[17]

Riociguat (BAY 63-2521) is the first orally available sGC stimulator. In clinical studies, oral riociguat was readily absorbed, exhibiting dose-proportional pharmacokinetics.[18,19] In patients with pulmonary arterial hypertension or distal chronic thromboembolic PH, single oral doses of riociguat were well tolerated and significantly improved pulmonary hemodynamics,[19] and longer-term administration of riociguat (1–2.5 mg 3 times daily) significantly improved exercise capacity and symptoms as well as hemodynamic parameters.[20] In recent randomized, controlled, phase 3 studies in patients with pulmonary arterial hypertension or chronic thromboembolic PH, riociguat (1–2.5 mg 3 times daily) improved 6-minute walk distance, compared with placebo, and also improved pulmonary vascular resistance (PVR), functional class, dyspnea, and health-related quality of life.[21,22] The aim of our pilot study (initiated before the phase 3 studies) was to evaluate the effects of a single dose of riociguat in COPD-associated borderline or manifest PH. Hemodynamic parameters, lung function, gas exchange, safety, and tolerability were assessed to inform future clinical development.

METHODS

Patients

Inclusion and exclusion criteria are summarized in Table 1. If clinically justified (i.e., if no adverse effect on the patient was anticipated), chronic medications (e.g., COPD-specific oral and inhaled therapies, blood pressure–lowering medications) were withheld on the morning of study drug administration and until study measurements were completed.

The study, undertaken in 6 centers in Germany, was conducted in accordance with the Declaration of Helsinki (modified in 2008) and adhered to the International Conference on Harmonisation Good Clinical Practice guideline and the German Drug Law. The local ethics committee at the principal investigator's site approved the protocol, and written informed consent was obtained from all patients.

Study design

This was an exploratory, nonrandomized, nonblinded, noncontrolled pilot study (www.clinicaltrials.gov: NCT00640315). Patients received a single dose of riociguat (1 or 2.5 mg, previously shown to be well tolerated[19]) in the morning of each of two separate assessment days at least 48 h apart. Hemodynamic parameters and blood gases were assessed on the first profile day and lung function on the second profile day. A planned safety assessment in the 1-mg group (n = 10) confirmed that the 1-mg dose was well tolerated before riociguat was administered to the 2.5-mg group (n = 12). In a

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
All of the following:	Any of the following:
Adults with suspected COPD-associated borderline or manifest PH (PH group 3.1[23]) and COPD of GOLD stages II–IV,[24] admitted to hospital for routine invasive diagnostics	Preexisting clinically relevant lung disease other than COPD
PH diagnosed on the basis of cardiac catheter data (PVR > 270 dyn·s·cm^{-5}, mean PAP ≥ 23 mmHg)[a]	Acute or severe chronic left heart failure
Stable disease with no exacerbation of COPD in the past month	Severe coronary artery disease
FEV_1/FVC < 70%	Uncontrolled arterial hypertension
PaO_2 > 50 mmHg	Severe left ventricular hypertrophy
$PaCO_2$ ≤ 55 mmHg	Congenital or acquired valvular or myocardial disease
	Systolic blood pressure < 100 mmHg
	Heart rate of <55 or >105 beats·min^{-1}
	Severe hepatic impairment (total bilirubin > 2 mg·dL^{-1} [34 μM])
	Severe renal impairment (serum creatinine > 2 mg·dL^{-1} [177 μM])
	History of previous therapeutic radiation of the lungs or mediastinum
	Concomitant use of specific phosphodiesterase inhibitors (e.g., sildenafil, vardenafil, or tadalafil), endothelin antagonists (e.g., bosentan or sitaxsentan), intravenous prostacyclin, or iloprost[b]

Note: COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAP: pulmonary artery pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance.

[a] Data obtained before administration of riociguat, or before administration of nitric oxide in a subset of patients who received inhaled nitric oxide before riociguat.

[b] If a patient was receiving any of these drugs before the study, a drug-specific wash-out period had to be considered.

subset of patients ($n = 8$), riociguat administration was preceded by short-term administration of inhaled NO.

Outcome measures

Hemodynamic parameters. The primary hemodynamic parameters recorded in the study were mean PAP and PVR. Secondary parameters were mean right atrial pressure, systolic and diastolic PAP, pulmonary capillary wedge pressure, heart rate, systemic blood pressure, cardiac output, PVR index, systemic vascular resistance, systemic vascular resistance index, and cardiac index. Measurements were obtained before riociguat administration and at 0.5, 1, 1.5, 2, 3, and 4 hours thereafter.

Lung function and gas exchange. The pulmonary function parameters measured were partial pressures of oxygen and carbon dioxide in arterial blood (PaO_2 and $PaCO_2$, respectively), venous partial oxygen pressure, arterial and venous oxygen saturation, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), total lung capacity, residual volume, maximal expiratory flow at 75%, 50%, and 25% of expiratory vital capacity, total airway resistance, vital capacity, diffusing capacity of the lung for carbon monoxide, alveolar volume, and specific diffusing capacity. All lung function parameters were measured or calculated at baseline and 2 and 6 hours after riociguat administration.

Pharmacokinetic parameters. Riociguat plasma concentrations were determined by a fully validated high-performance liquid chromatography–mass spectrometry assay, using blood samples obtained at regular intervals up to 36 hours after riociguat administration. Primary parameters included the following: area under the plasma concentration–versus-time curve from 0 to infinity (AUC); AUC divided by dose (mg), expressed per kilogram body weight (AUC_{norm}); maximum drug concentration in plasma after single-dose administration (C_{max}); and C_{max} divided by dose (mg), expressed per kilogram body weight ($C_{max,norm}$). Secondary parameters included time to reach maximum drug concentration in plasma (t_{max}) and the half-life associated with terminal elimination ($t_{1/2}$).

Safety measures

Adverse events (AEs), electrocardiogram data, and standard hematology and clinical chemistry parameters were recorded.

Statistical analysis

SAS statistical software, version 9.1 (SAS Institute, Cary, NC), was used for data analysis. A 2-sided t test was performed on the peak effects of hemodynamic variables. A nonadjusted P value of less than 0.05 was accepted as statistically significant. The chosen sample size of at least 8 patients per dose group was considered sufficient to fulfill the exploratory objectives of this study. Following riociguat administration, a significant change of 178 dyn·s·cm^{-5} from baseline PVR and 3.4 mmHg from baseline mean PAP could be detected with a power of 80%, assuming that the associated standard deviations did not exceed the values observed in a previous investigation: 154 dyn·s·cm^{-5} for PVR and 2.96 mmHg for mean PAP.

RESULTS

Twenty-three patients were recruited to the study and received riociguat 1 or 2.5 mg. Patient characteristics at baseline and hemodynamic measurements before administration of riociguat are shown in Table 2, and concomitant medications are shown in Table 3. One patient withdrew informed consent after the first assessment and was excluded from the pharmacodynamic and pharmacokinetic analyses. Few protocol deviations were noted, and it was deemed that the conclusions of the study were not affected by these deviations (in particular, 2 patients had PVR < 270 dyn·s·cm^{-5}, and one of these patients also had a mean PAP of 20 mmHg before treatment with any study drug). On the basis of hemodynamic measurements before treatment with any study drug, 2 patients had borderline PH (mean PAP: 21–24 mmHg), and 2 patients had severe PH (mean PAP ≥ 40 mmHg). All patients were being treated with bronchodilators at baseline, and the majority were also receiving treatment with agents acting on the renin-angiotensin system, diuretics, and/or oxygen.

Hemodynamic parameters

The peak effects of riociguat treatment and inhaled NO testing, compared with the respective pretreatment baselines, are shown in Table 4 and Figure 1. Statistically significant decreases were observed with both riociguat 1 mg and riociguat 2.5 mg for the primary parameters of mean PAP and PVR (Fig. 1). By contrast, the peak postbaseline effect of inhaled NO was significant only for mean PAP and not for PVR. Moreover, riociguat consistently and significantly reduced systemic blood pressure and systemic vascular resistance and significantly increased heart rate, cardiac output, and cardiac index.

Lung function and gas exchange

There was no change in lung function after administration of riociguat (Table 5). Overall, there were no clinically relevant changes in blood gas parameters (Table 5). Of 22 patients, 16 (72.7%; 8 in each dose group) received oxygen. A few patients had the oxygen supply adapted to their medical needs during the assessment of pharmacodynamic parameters.

Pharmacokinetic parameters

Following single oral doses of riociguat 1 or 2.5 mg, plasma concentrations of riociguat showed dose-dependent increases, with pronounced interindividual variability. The C_{max} values were reached after 0.9–7.8 hours, and the $t_{1/2}$ values were in the range 1.5–28 hours (Table 6). The C_{max} and AUC values for riociguat showed dose proportionality for the 1- and 2.5-mg doses. The relationship be-

Table 2. Patient characteristics in 22 patients evaluated for hemodynamics and lung function parameters

Characteristic	Riociguat 1 mg (n = 10)	Riociguat 2.5 mg (n = 12)
Demographic variables		
Female/male	5/5	6/6
Mean age, years (range)	67.5 (56–82)	69.3 (61–79)
Mean body mass index ± SD, $kg \cdot m^{-2}$	27.28 ± 4.87	26.48 ± 3.84
White	10	12
Hemodynamic variables assessed by right heart catheterization before administration of riociguat, mean (range)		
Pulmonary artery pressure, mean, mmHg	28.0 (20–48)	31.7 (21–48)
Cardiac output, $L \cdot min^{-1}$	4.63 (3.58–5.46)	4.94 (3.80–6.25)
Pulmonary vascular resistance, $dyn \cdot s \cdot cm^{-5}$	353 (151–595)	370 (205–505)
Systolic blood pressure, mmHg	140 (103–187)	136 (110–166)
Diastolic blood pressure, mmHg	70 (61–84)	66 (52–82)
Heart rate, $beats \cdot min^{-1}$	73 (46–93)	72 (53–92)
Blood gases at baseline, mean (range)[a]		
PaO_2, mmHg	85.6 (55.1–129)	71.6 (51.7–104)
$PaCO_2$, mmHg	46.7 (27.6–72.4)	42.3 (28.9–58.0)
SaO_2, %	94.6 (85.8–98.6)	93.1 (87.9–98.1)
SvO_2, %	70.0 (59.5–76.2)	66.7 (59.0–71.0)
Lung function at baseline, mean (range)		
FEV_1, % of predicted	43.1 (15.4–81.9)	41.2 (25.0–84.1)
FEV_1/FVC, %	59.6 (26.2–85.1)	48.6 (36.9–67.3)
D_LCO, $mmol \cdot min^{-1} \cdot kPa^{-1}$	2.3 (0.95–4.31)	2.42 (1.20–3.96)
Airway resistance, $kPA \cdot s \cdot L^{-1}$	0.87 (0.35–2.89)	0.78 (0.25–1.43)
Residual volume, % of predicted	218 (116–315)	198 (64.9–285)

Note: D_LCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; SaO_2: oxygen saturation in arterial blood; SD: standard deviation; SvO_2: oxygen saturation in venous blood.

[a] Sixteen of the patients (8 in each treatment group) received supplemental oxygen.

tween riociguat plasma concentration and PVR and systemic vascular resistance is illustrated in Figure 2.

Safety measures

Treatment-emergent AEs occurred in 4 patients (40%) in the 1-mg dose group and in 6 patients (46%) in the 2.5-mg dose group and were of mild or moderate intensity. The moderate AEs included anemia, ventricular extrasystoles, nausea, vomiting, respiratory tract infection, and dizziness. There were 2 serious AEs that were also moderate in severity: infective exacerbation of COPD and pneumonia. Both of these events were assessed by the investigators as being unrelated to the study drug. All events had resolved by the end of the study, apart from one case of moderate anemia and one case of mild renal impairment, both of which had shown improvement. Five treatment-emergent AEs were considered drug related by the investigators: mild visual impairment, dizziness, and renal impairment (minor and transient increase in serum creatinine in one patient with preexisting kidney disease) and moderate nausea and dizziness. No deaths occurred during the study.

Treatment-emergent abnormal laboratory values were clinically irrelevant or associated with coexisting diseases, such as diabetes

Table 3. Concomitant medications in 23 patients valid for safety analysis

Characteristic	Riociguat 1 mg (n = 10)	Riociguat 2.5 mg (n = 13)
Antithrombotic agents	5	10
Diuretics	6	11
Digitoxin	1	4
β-blockers	3	6
Agents acting on the renin-angiotensin system	8	11
Bronchodilators	10	13
Oxygen	8	9

Table 4. Hemodynamic response to inhaled nitric oxide and riociguat

Parameter, treatment	Patients, *n*	Peak postbaseline effect[a]		
		Mean	SD	*P* value[b]
Mean PAP, mmHg[c]				
iNO 20 ppm	8	−3.88	2.90	0.0069[d]
Riociguat 1 mg	10	−3.60	3.41	0.0086[d]
Riociguat 2.5 mg	12	−4.83	4.17	0.0020[d]
PVR, dyn·s·cm^{-5}[c]				
iNO 20 ppm	7	−57.14	78.64	0.1029
Riociguat 1 mg	10	−58.32	50.46	0.0053[d]
Riociguat 2.5 mg	11	−123.8	73.53	0.0002[d]
Mean RAP, mmHg				
iNO 20 ppm	8	1.25	1.28	0.0282[d]
Riociguat 1 mg	9	−2.00	1.41	0.0028[d]
Riociguat 2.5 mg	11	−0.64	1.69	0.2400
PCWP, mmHg				
iNO 20 ppm	8	−0.13	1.73	0.8436
Riociguat 1 mg	10	−3.60	3.57	0.0110[d]
Riociguat 2.5 mg	12	−1.17	3.38	0.2570
Cardiac output, L·min^{-1}				
iNO 20 ppm	7	−0.03	0.40	0.8627
Riociguat 1 mg	10	0.66	0.48	0.0018[d]
Riociguat 2.5 mg	11	1.61	1.49	0.0049[d]
Cardiac index, L·min·m^{2}[c]				
iNO 20 ppm	7	−0.02	0.20	0.8136
Riociguat 1.0 mg	10	0.35	0.26	0.0020[d]
Riociguat 2.5 mg	11	0.89	0.83	0.0051[d]
SVR, dyn·s·cm^{-5}				
iNO 20 ppm	7	39.77	168.04	0.5542
Riociguat 1 mg	9	−440.00	205.78	0.0002[d]
Riociguat 2.5 mg	10	−467.70	154.94	<0.0001[d]
Heart rate, beats·min^{-1}				
Riociguat 1 mg	10	9.40	7.31	0.0028[d]
Riociguat 2.5 mg	12	13.92	8.68	0.0002[d]
Systolic BP, mmHg				
Riociguat 1 mg	10	−26.30	16.63	0.0007[d]
Riociguat 2.5 mg	12	−22.17	15.24	0.0004[d]
Diastolic BP, mmHg				
Riociguat 1 mg	10	−13.50	6.84	0.0002[d]
Riociguat 2.5 mg	12	−11.25	9.50	0.0017[d]
MAP, mmHg				
Riociguat 1 mg	10	−17.10	7.71	0.0001[d]
Riociguat 2.5 mg	12	−13.92	8.03	0.0001[d]

Note: BP: blood pressure; iNO: inhaled nitric oxide; MAP: mean arterial pressure; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SD: standard deviation; SVR: systemic vascular resistance.

[a] Peak postbaseline effect means the largest decrease or smallest increase for pressure and resistance measurements and the largest increase or smallest decrease for cardiac output, cardiac index, and heart rate measurements.

[b] *t* test.

[c] Source data for Figure 1.

[d] Statistically significant at the 5% significance level.

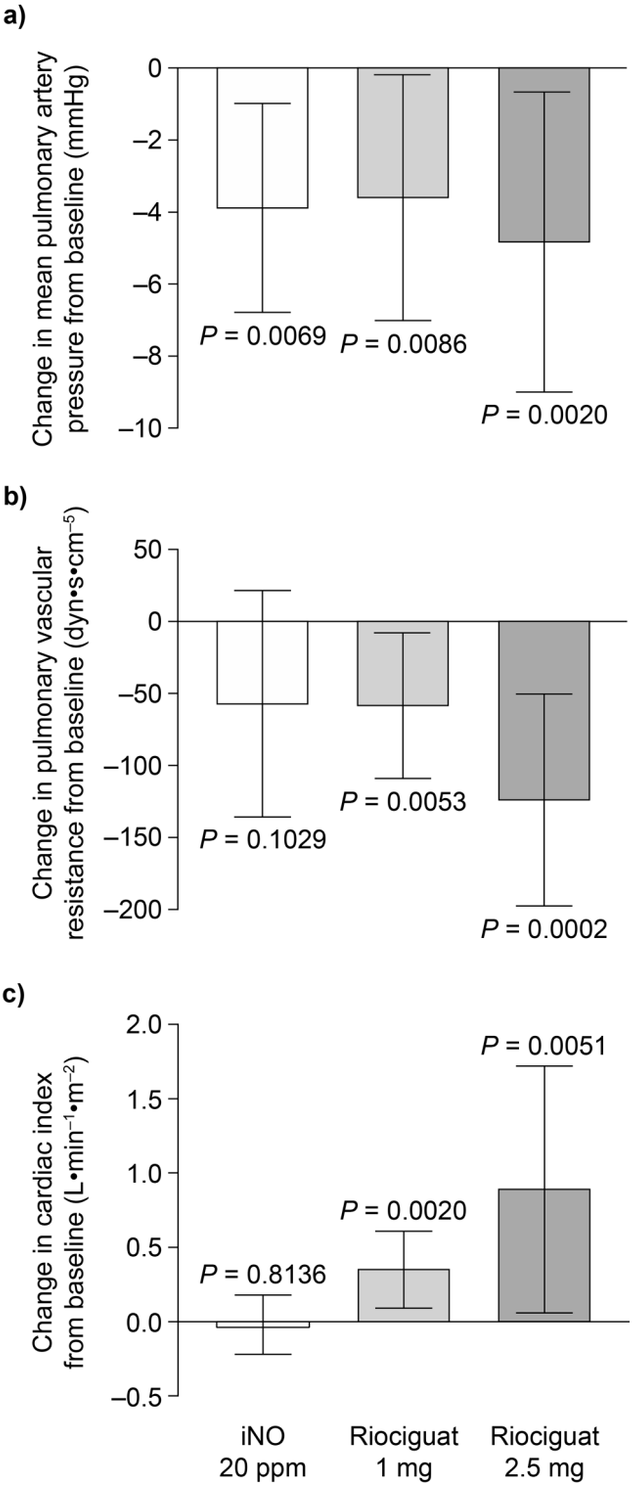

Figure 1. Effect of inhaled nitric oxide (iNO) and riociguat on mean pulmonary artery pressure (*a*), pulmonary vascular resistance (*b*), and cardiac index (*c*). Data are presented as mean ± standard deviation. See Table 4 for source data.

mellitus, and were not related to the study drug. Electrocardiogram findings, in particular mean changes in QTc from baseline to any of the subsequent time points, were not clinically relevant.

DISCUSSION

This pilot study is the first to investigate the effect of a single dose of riociguat in COPD-associated borderline or manifest PH (mean PAP ≥ 23 mmHg). Although the study involved a relatively small number of patients, riociguat 1 and 2.5 mg significantly decreased mean PAP and PVR and improved cardiac output. These results add to those reported in studies of riociguat in patients with pulmonary arterial hypertension or distal chronic thromboembolic PH.[19] The short-term favorable effects of riociguat suggest that a longer-term, placebo-controlled study of this agent in COPD-associated PH is warranted.

A recent preclinical study showed that riociguat can prevent PH, vascular remodeling, and right ventricular hypertrophy in a mouse model of lung emphysema induced by chronic exposure to tobacco smoke.[25] In our clinical study, the acute hemodynamic effects of riociguat were generally more pronounced than those observed after administration of inhaled NO. The data are consistent with a previous study in which NO inhalation alone caused nonsignificant changes in PVR[26] and with the fact that a substantial proportion of patients with PH do not respond to inhaled NO in acute vasodilator tests.[1] Riociguat produced pulmonary vasodilation and reduced systemic blood pressure and systemic vascular resistance without relevant adverse effects after single doses, and it significantly improved cardiac output from baseline. An increase in heart rate was observed, suggesting that the improvement in cardiac output could reflect sympathetic activation of the heart in response to the reduction in systemic blood pressure. It is unclear whether such an effect would also occur with long-term riociguat treatment in this patient group: patients with pulmonary arterial hypertension or chronic thromboembolic PH also showed a mean increase in heart rate from baseline following a single dose of riociguat,[19] but such a change was not observed after long-term riociguat administration in phase 3 studies, although cardiac output was still improved.[21,22] Overall, single doses of riociguat were well tolerated in our study. The pharmacokinetic results were similar to those seen in patients with other forms of PH.[19]

A practical treatment for PH in the context of COPD is lacking, with the risk of worsening gas exchange posing a challenge for available PH therapies.[27] In our study, PaO_2 showed mean changes from baseline of −10.9 to −15.2 mmHg, with large standard deviations (14.0–26.6 mmHg), following administration of single doses of riociguat. Previously, a significant fall in PaO_2 was observed following a 48-hour intravenous infusion of prostacyclin in patients with severe COPD complicated by acute respiratory failure and PH.[28] Blood gases were maintained following inhalation of two 2.5-μg doses of iloprost in patients with COPD and PH,[29] but a more recent placebo-controlled study found that single doses of iloprost (10 or 20 μg) caused a significant reduction in oxygen saturation at rest.[30] In a single-dose study of sildenafil in patients with COPD-associated PH, PaO_2 decreased from baseline at rest

Table 5. Lung function and gas exchange parameters (predose values and change at 2 h after dose)

		Predose		Change 2 h after dose		Change 2 h after dose, %	
Parameter, riociguat dose group	No. of patients predose/ after dose	Mean	SD	Mean	SD	Mean	SD
FEV_1, % predicted							
1 mg	9/9	43.1	21.4	1.1	1.8	3.0	3.4
2.5 mg	12/11	41.2	18.2	1.3	5.0	4.4	11.9
FVC, % predicted							
1 mg	8/8	72.1	20.3	−0.6	7.0	−0.4	8.0
2.5 mg	12/11	67.1	19.8	4.3	13.0	8.7	23.8
FEV_1/FVC, %							
1 mg	9/9	59.6	21.1	−0.3	8.1	−0.7	11.3
2.5 mg	12/11	48.6	9.7	−0.7	9.5	−1.3	18.0
PaO_2, mmHg							
1 mg	10/10	85.6	25.8	−15.2	26.6	−12.6	24.8
2.5 mg	10/9	71.6	18.7	−10.9	14.6	−13.0	14.0
$PaCO_2$, mmHg							
1 mg	10/10	46.7	11.4	0.7	6.6	4.4	20.9
2.5 mg	10/9	42.3	10.3	0.9	4.6	4.0	13.3

Note: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; SD: standard deviation.

(−6 mmHg [95% confidence interval: −8 to −4 mmHg]) but not during exercise.[31] Similar findings were observed following inhalation of NO (40 ppm) in patients with COPD.[32,33] The effects of sildenafil and NO on PaO_2 at rest were accompanied by a worsening of ventilation-perfusion mismatch, considered to result from inhibition of hypoxic vasoconstriction. We found no clinically relevant changes in blood gas parameters in our single-dose study, despite production of consistent and strong pulmonary vasodilation. Nevertheless, further research will be required to clarify the effect of riociguat on gas exchange.

The patients enrolled in our study had suspected PH and required right heart catheterization as part of the diagnostic process; a right heart catheter was therefore in place independently of the study. No complications of right heart catheterization were observed during the study. Right heart catheterization remains the gold standard for diagnosis of PH in this patient population; the

Table 6. Pharmacokinetic characteristics of riociguat in plasma

		Riociguat 1 mg (n = 10)			Riociguat 2.5 mg (n = 12)		
Parameter	Unit	Geometric mean	CV, %	Range	Geometric mean	CV, %	Range
AUC	$\mu g \cdot h \cdot L^{-1}$	481.9	65.3	90.10–1,533	1,319	56.8	351.4–3,389
AUC_{norm}	$kg \cdot h \cdot L^{-1}$	35.53	62.6	5.136–88.60	38.85	56.7	9.744–97.45
C_{max}	$\mu g \cdot L^{-1}$	42.96	32.3	25.93–90.65	116.0	36.0	43.90–221.4
$C_{max,norm}$	$kg \cdot L^{-1}$	3.185	27.0	1.670–5.106	3.419	30.9	1.457–5.758
t_{max}, median	Hours	1.750	. . .	0.917–4.000	1.742	. . .	1.000–7.750
$t_{1/2}$	Hours	8.422	58.6	1.519–28.06	9.541	50.7	2.587–26.69

Note: AUC: area under the plasma concentration–versus-time curve from 0 to infinity after a single dose; AUC_{norm}: AUC divided by dose (mg), expressed per kilogram body weight; C_{max}: maximum drug concentration in plasma after single-dose administration; $C_{max,norm}$: C_{max} divided by dose (mg), expressed per kilogram body weight; CV: coefficient of variation (geometric); t_{max}: time to reach maximum drug concentration in plasma; $t_{1/2}$: half-life associated with terminal elimination.

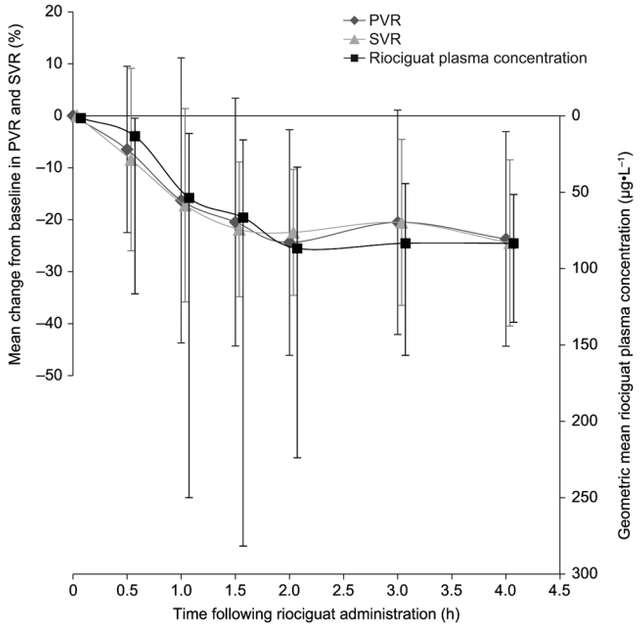

Figure 2. Changes over time in riociguat plasma concentration and pulmonary and systemic vascular resistance in patients receiving a single dose of riociguat (2.5 mg). Error bars show standard deviation. PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.

best noninvasive test is Doppler echocardiography, which can suggest the presence of PH, but right heart catheterization is necessary to confirm the diagnosis.[34]

Limitations of this exploratory pilot study include its small size and uncontrolled, open-label design. Single doses were studied, rather than the dose-titration regimen used in clinical practice. The main aim of this study was to investigate the hemodynamic dose-response effect during the first hours after riociguat administration. This information was considered a prerequisite for any future study of long-term treatment with dose titration in patients with COPD-associated PH. The majority of the patients received supplemental oxygen, but the method of oxygen supply and the fraction of inspired oxygen at the time of blood gas analysis were not recorded. The use of oxygen may have inhibited hypoxic vasoconstriction at baseline, which could have reduced the effect of riociguat on gas exchange. In addition, 2 patients in the study were considered to have borderline PH, at baseline (mean PAP of 24 mmHg), and 2 additional patients were included who did not meet all the criteria for borderline or manifest PH at baseline. The mean PAP threshold for inclusion in this study was set at 23 mmHg (rather than the threshold of 25 mmHg specified in general PH guidelines)[1,35] because PH associated with COPD is usually mild or moderate, with lower mean PAP levels than in idiopathic pulmonary arterial hypertension.[5] It could be speculated that the inclusion of patients with borderline PH might limit the potential for further reduction in PAP upon treatment and thus reduce the observed efficacy of the study drug. However, the majority of the patients had manifest PH (mean PAP $\geq$ 25 mmHg), and the few protocol deviations and the inclusion of 2 patients with borderline PH were not deemed to affect the conclusions.

In summary, this pilot study demonstrates favorable effects of single oral doses of riociguat 1 and 2.5 mg on hemodynamics in COPD-associated PH, without untoward effects on gas exchange or lung function. Single doses of riociguat were well tolerated in patients with COPD-associated PH. Therefore, a placebo-controlled study of the longer-term effects of riociguat in these patients is warranted.

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