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Riociguat treatment in patients with pulmonary arterial hypertension: Final safety data from the EXPERT registry

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ABSTRACT

Objective: The soluble guanylate cyclase stimulator riociguat is approved for the treatment of adult patients with pulmonary arterial hypertension (PAH) and inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension following Phase 3 randomized trials. The EXPosurE Registry RiociguaT in patients with pulmonary hypertension (EXPERT) study was designed to monitor the long-term safety of riociguat in clinical practice.

Methods: EXPERT was an international, multicenter, prospective, uncontrolled, non-interventional cohort study of patients treated with riociguat. Patients were followed for at least 1 year and up to 4 years from enrollment or until 30 days after stopping riociguat treatment. Primary safety outcomes were adverse events (AEs) and serious adverse events (SAEs) coded using Medical Dictionary for Regulatory Activities preferred terms and System Organ Classes version 21.0, collected during routine clinic visits (usually every 3–6 months) and collated via case report forms.

Results: In total, 326 patients with PAH were included in the analysis. The most common AEs in these patients were dizziness (11.7%), right ventricular (RV)/cardiac failure (10.7%), edema/peripheral edema (10.7%), diarrhea (8.6%), dyspnea (8.0%), and cough (7.7%). The most common SAEs were RV/cardiac failure (10.1%), pneumonia (6.1%), dyspnea (4.0%), and syncope (3.4%). The exposure-adjusted rate of hemoptysis/pulmonary hemorrhage was 2.5 events per 100 patient-years.

Conclusion: Final data from EXPERT show that in patients with PAH, the safety of riociguat in clinical practice was consistent with clinical trials, with no new safety concerns identified and a lower exposure-adjusted rate of hemoptysis/pulmonary hemorrhage than in the long-term extension of the Phase 3 trial in PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a form of pulmonary hypertension (PH) characterized by increased pulmonary vascular resistance (PVR) due to progressive remodeling of the pulmonary vasculature and can ultimately lead to death due to right heart failure [1–3]. PAH is characterized hemodynamically by precapillary PH, defined most recently [3] by a mean pulmonary arterial pressure $\geq$ 20 mmHg (previously $\geq$ 25 mmHg) [4], a pulmonary artery wedge pressure $\leq$ 15 mmHg and PVR $\geq$ 3 Wood units in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH), or other rare diseases [4].

Approved targeted therapies for PAH include prostacyclin analogs, a prostacyclin receptor agonist, endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5i), and the soluble guanylate cyclase stimulator, riociguat [4,5]; calcium channel blockers are also occasionally used for treatment of selected patients with PAH [4], although they are not generally described as PH-targeted drugs. Riociguat is approved for the treatment of adults with PAH and inoperable or persistent/recurrent CTEPH [6,7] based on robust efficacy and safety data from two Phase 3, randomized, placebo-controlled trials–Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial-1 (PATENT-1) [8] and Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial-1 (CHEST-1) [9], respectively–and their long-term extension studies PATENT-2 [10,11] and CHEST-2 [12,13].

EXPosurE Registry RiociguaT in patients with PH (EXPERT) was a prospective, non-interventional registry to monitor the long-term safety of riociguat in clinical practice.

2. Methods

2.1. Study design

EXPERT (NCT02092818) was an international, multicenter, prospective, uncontrolled, non-interventional cohort study of patients treated with riociguat in 28 countries (see supplement for list). EXPERT was linked with the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA [https://compera.org/], one of the largest global academic PH registries. This was consistent with guidance from regulatory authorities to utilize existing registries.

Patients were followed for 1–4 years from enrollment (including post-treatment follow-up for safety events) during a recruitment period of 3 years or until 30 days after stopping riociguat treatment. Data were collected using a case report form (CRF) based on the COMPERA CRF extended to obtain riociguat safety data. Results were collected during routine clinical follow-up visits, usually every 3–6 months. EXPERT ran from May 2014 (first patient, first visit) to March 2018 (last patient, last visit) and was conducted in accordance with good pharmacovigilance practices. Protocol approvals from independent ethics committees or institutional review boards at all participating centers were obtained. EXPERT was not requested but was accepted by the European Medicines Agency for the collection of additional long-term post-approval data on riociguat.

2.2. Patients

Patients with PH who started treatment or were already being treated with riociguat were eligible for inclusion. Patients participating in an interventional clinical trial were excluded. The protocol asked for the indications (PAH and CTEPH) for riociguat to be considered; however, 48 patients with PH in Groups 2, 3, or 5 of the international classification of PH [14] (for which riociguat is not licensed ["other PH"]) were enrolled.

Patients with disease duration $\geq$6 months were defined as prevalent, and those diagnosed within <6 months of enrollment were defined as incident. Patients were defined as riociguat-pretreated if they had been receiving riociguat for $\geq$3 months before registry entry and as riociguat-newly treated if they had been receiving riociguat for <3 months before registry entry. Riociguat-newly treated patients were therefore not necessarily incident patients and could have received PAH-approved therapy before riociguat. Newly treated patients were further categorized as switched or non-switched. Switched patients were newly treated patients who had stopped prior therapy $\leq$10 days before commencing riociguat.

2.3. Data collection

The following data were collected at baseline: demographics, medical history, comorbidities, adverse events (AEs), disease history, pregnancy, history of smoking, 6-min walking distance (6MWD), World Health Organization functional class (WHO FC), Borg Dyspnea Index, EuroQoL 5-dimensional Visual Analog Score (EQ-5D VAS), hemodynamic parameters from right heart catheterization, biomarkers (*N*-terminal prohormone of brain natriuretic peptide and brain natriuretic

peptide), laboratory variables, riociguat dose, and prior or concomitant PAH-approved therapy. PH etiology was collected according to the Dana Point Classification 2008 [15] but is shown in this report in terms of the Nice Classification, 2013 [14]. The following were documented at each follow-up visit: AEs; changes in treatment; changes of demographics, pregnancy, and smoking status; 6MWD; WHO FC; Borg Dyspnea Index; EQ-5D VAS; hemodynamic parameters; biomarkers; laboratory variables; and riociguat dose.

2.4. Safety assessments

The primary safety outcomes were AEs and serious adverse events (SAEs) coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and System Organ Classes version 21.0. An AE was considered serious if it: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of hospitalization (with specific exceptions, defined in the protocol), resulted in persistent or significant disability or incapacity, was a congenital abnormality or birth defect, or was medically important. Secondary safety outcomes included AEs and SAEs of special interest (hypotension and hemoptysis/pulmonary hemorrhage). The outcomes of all AEs and SAEs were followed up and documented. Where required, study staff contacted the investigators to obtain further information. This report focuses on AEs and SAEs occurring during the treatment phase (onset date $\leq$ 2 days after the most recent dose of riociguat). Deaths were analyzed in terms of all SAEs with a fatal outcome with onset during the treatment phase and the post-treatment phase (onset date $>$ 2 days after discontinuation until the end of the 30-day safety follow-up).

2.5. Statistical methods and populations analyzed

Planned enrollment for the entire study was 900 patients. This allowed for the detection of $\geq$3 "uncommon" AEs with an incidence $\geq$0.5%. EXPERT was an observational study. All variables and outcomes, including comparisons between predefined groups (such as newly treated versus pretreated patients, and prevalent versus incident patients) were analyzed descriptively. Statistical analyses of these comparisons were not performed because they would be of limited value without adjustment for differences between the groups. All analyses were performed with SAS 9.3. Categorical variables were analyzed using frequency tables and continuous variables by summary statistics (mean $\pm$ standard deviation [SD], median, and minimum–maximum range). Survival rates were estimated from Kaplan−Meier plots. The evaluable population consisted of all enrolled patients who did not withdraw consent and had received at least one dose of riociguat with dosing data available.

3. Results

3.1. Types of PH enrolled

The entire evaluable population consisted of 1330 patients: 326 with PAH, 956 with CTEPH, and 48 with "other PH." The EXPERT study therefore exceeded its planned enrollment by over 400 patients. In view of the differences between PAH and CTEPH in pathophysiology, treatment, and outcomes, it was decided to analyze and present results separately for the two conditions. This report concentrates on patients with PAH with results in CTEPH described in a separate publication [29]. Results for the patients with "other PH" are not discussed further as riociguat is not indicated for these patients, the sample size was too small to permit conclusions, and the characteristics of this patient group varied widely due to the mix of PH entities.

3.2. PAH patient disposition

The evaluable population with PAH consisted of 326 patients: 182 (55.8%) riociguat-pretreated and 144 (44.2%) riociguat-newly treated. Approximately 87% of patients completed the study (Fig. 1).

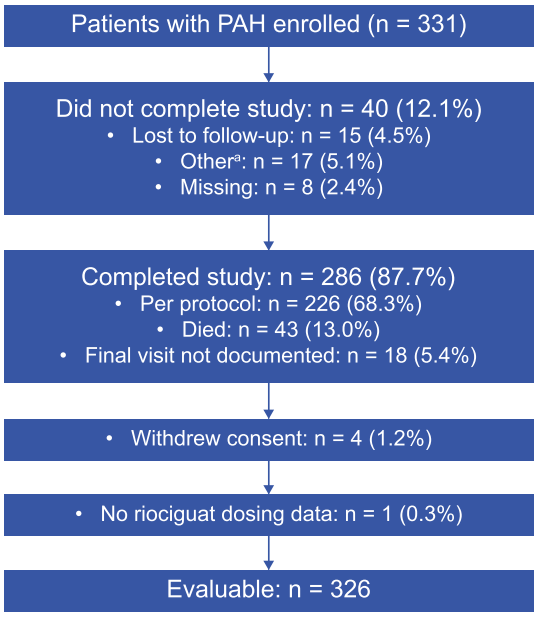

Fig. 1. Patient disposition.
PAH, pulmonary arterial hypertension. The numbers and percentages refer to the total PAH population enrolled (n = 331).
Chart shows primary reason for discontinuation.
[a]Other reasons for not completing the study are listed in Supplementary Table 1.

3.3. Demographics and baseline characteristics

The mean age of the patients was 54.0 $\pm$ 16.5 years, with a median interquartile range (IQR) disease duration of 3.4 (0.8–6.7) years; 234 patients (71.8%) were women. PAH was prevalent in 254 patients (77.9%), incident in 61 (18.7%), and unknown in 11 (3.4%). At baseline, riociguat was used in combination with ERAs alone in 183 patients (56.1% [bosentan, 23.3%; macitentan, 22.1%; ambrisentan, 10.7%]), with prostanoids alone in 12 (3.7% [iloprost, 2.2%; intravenous treprostinil, 1.2%; inhaled epoprostenol, 0.3%]), and with both classes in 43 (13.2%). No patient received concomitant PDE5i. At Visit 6 (month 33−<39), 3 years, 86.6% of patients were receiving combination therapy. Approximately 90% of patients had at least one comorbidity. Other baseline demographics are shown in Table 1. Most patients (69.3%) had idiopathic PAH (Fig. 2).

3.4. Riociguat safety

3.4.1. Total population

The median (range) duration of observation and riociguat treatment was 472.5 (0.0–1381.0) days and 467.0 (0.0–1381.0) days, respectively. In total, 229 patients with PAH (70.2%) experienced AEs and 152 (46.6%) experienced SAEs. These events were considered drug-related by the investigator in 49 patients (15.0%) and 23 patients (7.1%), respectively. The most common AEs and SAEs are shown in Table 2. Discontinuation due to AEs and SAEs occurred in 24 (7.4%) and 21 (6.4%) patients, respectively. The most common AEs leading to discontinuation were right ventricular (RV) failure/cardiac failure and dyspnea, each in four patients (1.2%), hypotension in three patients (0.9%), and hemoptysis in two patients (0.6%). The most common SAEs leading to discontinuation were RV failure/cardiac failure and dyspnea, each in four patients (1.2%). Safety data for patients according to use of riociguat as monotherapy or in combination with other PAH-specific

Table 1
Baseline demographics and disease characteristics (n = 326).

Characteristic	Mean ± SD or number (%)	Characteristic	Mean ± SD or number (%)
Age, years	54.0 ± 16.5	Riociguat daily dose at initial study visit, mg	
Age group, years		Mean	6.8 ± 1.3 (n = 322)
<65	236 (72.4)	Median (range)	7.5 (1.5–7.5) (n = 322)
65 to < 75	51 (15.6)		
≥75	39 (12.0)		
BMI, kg/m^2	27.0 ± 11.8	Riociguat median daily dose at initial study visit (mg)	
BMI category, kg/m^2		≤2.5	3 (0.9)
<18.5	13 (4.0)	>2.5 to 4.5	32 (9.8)
18.5 to < 25	137 (42.0)	>4.5 to 6	57 (17.5)
25 to < 30	96 (29.4)	>6 to 7.5	230 (70.6)
≥30	80 (24.5)	Missing	4 (1.2)
Smoking status		Concomitant CCB	22 (6.7)
Never	218 (66.9)		
Former	91 (27.9)	Concomitant anticoagulation therapy	
Current	17 (5.2)	Oral anticoagulation	161 (49.4)
Age at initial PH diagnosis, years	48.9 ± 17.2 (n = 316)	Vitamin K antagonist	111 (34.0)
Median (IQR) disease duration, years	3.4 (0.8–6.7) (n = 316)	Direct oral anticoagulant	37 (11.3)
		Other oral anticoagulation[b]	12 (3.7)
		Other anticoagulant[b]	7 (2.1)
		Concomitant antiplatelet agents	41 (12.6)
WHO FC, % (I/II/III/IV/unknown)	4.0/33.4/49.4/6.7/6.4	Comorbidity	
BNP, pg/mL (median, range)	150 (5.8–1305) (n = 57)	At least one medical history finding	293 (89.9)
NT-proBNP, pg/mL (median, range)	437 (12–79 080) (n = 132)	Arterial hypertension	115 (35.3)
6MWD, m	386 ± 132 (n = 282)	Thyroid disease	80 (24.5)
6MWD		Diabetes mellitus	50 (15.3)
<320 m[a]	76 (23.3)	Coronary heart disease	47 (14.4)
≥320 m	206 (63.2)	Obstructive sleep apnea	31 (9.5)
<380 m[a]	122 (37.4)	Venous thromboembolism	25 (7.7)
≥380 m	160 (49.1)	Cancer	20 (6.1)
Missing	44 (13.5)	History of hemoptysis/lung bleeding	8 (2.5)
EQ-5D VAS	60.0 ± 22.4 (n = 113)	Other	250 (76.7)
Borg Dyspnea Index	4.1 ± 2.4 (n = 252)		
mPAP, mmHg	51.8 ± 14.6 (n = 282)		
PVR, dyn·s·cm^{-5}	822 ± 529 (n = 261)		
PAWP, mmHg	10.4 ± 5.3 (n = 270)		
Cardiac index, L/min/m^2	2.5 ± 1.2 (n = 245)		
RAP, mmHg	9.3 ± 6.5 (n = 211)		
SvO_2 (%)	64.0 ± 11.3 (n = 211)		

6MWD, 6-min walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; EQ-5D VAS, EuroQoL 5-dimensional Visual Analog Score; IQR, interquartile range; mPAP, mean pulmonary artery pressure; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SvO_2, saturated venous oxygen; WHO FC, World Health Organization functional class.
Data are mean ± SD or number (%) unless otherwise stated.
Results are for all patients with PAH (n = 326) unless otherwise stated.
[a] Thresholds chosen (380 m prespecified) based on available (6MWD) cohort data at the time indicating good or poor prognosis [16,17].
[b] As indicated by the investigator on the CRF.

drugs are shown in Supplementary Table 2. Overall, rates of AEs were slightly higher in the three combination therapy subgroups (66.7–74.3%) than with riociguat monotherapy (61.4%).

Hemorrhages were reported in 41 patients (12.6%) and serious hemorrhages in 17 patients (5.2%). The most frequently occurring hemorrhages were epistaxis in 11 patients (3.4%), hemoptysis in eight patients (2.5%), and hemoglobin decreased in six patients (1.8%); pulmonary hemorrhage was not reported. The most common serious hemorrhages were hemoptysis (n = 6; 1.8%), and gastrointestinal hemorrhage and hematemesis, each in two patients (0.6%). Of all patients with hemorrhages, six were recorded as receiving non-vitamin K antagonist anticoagulants (NOACs) and 16 as receiving vitamin K antagonists (VKAs). Hemoptysis was considered an AE of special interest and is discussed further below.

3.4.2. Safety in prevalent versus incident patients

A post hoc analysis compared prevalent patients (disease duration ≥ 6 months) (n = 254) with incident PAH patients (diagnosed within <6 months of enrollment) (n = 61) according to disease duration data available at baseline. Disease characteristics, including 6MWD and WHO FC, suggested a more severe disease status in incident patients compared with prevalent patients (data not shown). Median (range) disease duration was 1.4 (0.0–5.1) months in incident patients and 4.6 (0.5–49.6) years in prevalent patients. AEs were reported in 175 prevalent (68.9%) patients and 45 incident patients (73.8%), and SAEs in 112 (44.1%) and 32 (52.5%), respectively.

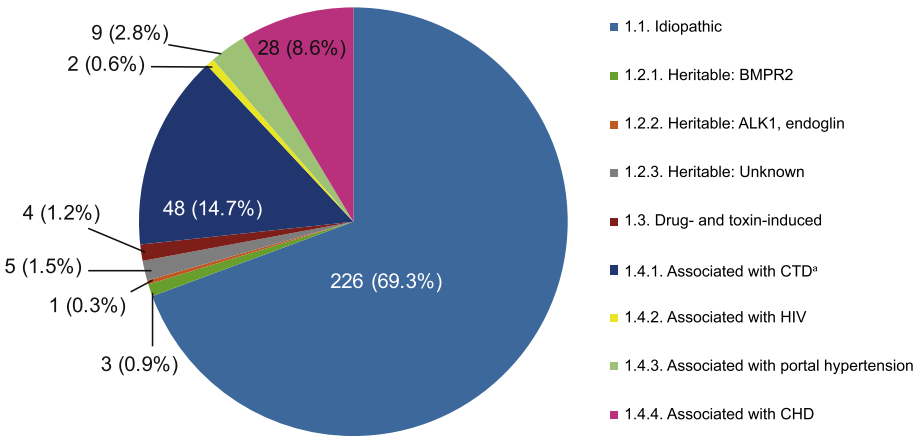

Fig. 2. PAH etiology according to Nice classification 2013 [14].
ALK1, activin receptor-like kinase 1; BMPR2, bone morphogenetic protein receptor type II; CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.
[a]CTD includes systemic sclerosis (9.8%), systemic lupus erythematosus (1.8%), mixed CTD (0.9%), undifferentiated CTD (0.9%), other autoimmune rheumatic diseases (0.9%), and overlap (fulfilling two criteria) 0.3%.

3.4.3. Comparison between riociguat-pretreated and riociguat-newly treated patients

Compared with riociguat-pretreated patients, riociguat-newly treated patients had a shorter disease duration, shorter 6MWD, a higher proportion of WHO FC III/IV disease, and a greater proportion of incident disease (Table 3). Approximately 90% of patients in both groups had at least one comorbidity. Approximately 88% of patients in both groups completed the study (Fig. 3). Of the riociguat-newly treated patients, 33 (22.9%) had been switched from previous PAH-approved therapy, including 31 (21.5%) switched from PDE5i, 4 (2.8%) from a prostanoid, and 1 (0.7%) from an ERA (a few patients were switched from more than one prior therapy).

Table 2
Most common AEs and SAEs in the total population (n = 326).

AEs[a]	n (%)
Dizziness	38 (11.7)
Diarrhea	28 (8.6)
Dyspnea	26 (8.0)
Cough	25 (7.7)
RV failure/cardiac failure	35 (10.7)[b]
Peripheral edema/edema	35 (10.7)[c]
Pneumonia	22 (6.7)
Nasopharyngitis	19 (5.8)
SAEs[d]	**n (%)**
RV failure/cardiac failure	33 (10.1)[e]
Pneumonia	20 (6.1)
Dyspnea	13 (4.0)
Syncope	11 (3.4)
PAH[f]	11 (3.4)
PH[f]	10 (3.1)
Respiratory tract infection	9 (2.8)
Death (cause unknown)[g]	9 (2.8)
Atrial fibrillation	8 (2.5)
Acute kidney injury	8 (2.5)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RV, right ventricular; SAE, serious adverse event; WHO FC, Word Health Organization functional class; 6MWD, 6-min walking distance.
Note. Patients with peripheral edema/edema, or RV failure/cardiac failure, could have both events.
[a] Preferred-term AEs reported in ≥5% of patients.
[b] Including RV failure in 25 patients (7.7%) and cardiac failure in 10 patients (3.1%).
[c] Including edema in 13 patients (4.0%) and peripheral edema in 22 patients (6.7%).
[d] Preferred-term SAEs reported in ≥2% of patients.
[e] Including RV failure in 25 patients (7.7%) and cardiac failure in 8 patients (2.5%).
[f] Preferred term for worsening of condition.
[g] Cases with MedDRA preferred term, "Death" under MedDRA system organ class, "General Disorders and Administration Site Condition" with AE lowest level term, "Unknown cause of death."

AEs were reported in 122 riociguat-pretreated patients (67.0%) and 107 riociguat-newly treated patients (74.3%). SAEs were reported in 74 patients (40.7%) and 78 patients (54.2%), respectively. Numerically more AEs and SAEs in riociguat-newly treated patients were considered drug-related and led to drug discontinuation than in riociguat-pretreated patients (Table 4). Most individual AEs and SAEs were numerically more frequent in newly treated patients. The most common AEs and SAEs leading to discontinuation are shown in Supplementary Table 3. Safety results in switched patients were generally similar to those seen in non-switched patients (data not shown). In both riociguat-pretreated and riociguat-newly treated patients, there was a slightly higher incidence of AEs with combination therapy compared with monotherapy (Supplementary Table 4).

3.5. AEs and SAEs of special interest

AEs and SAEs of special interest were numerically more frequent in riociguat-newly treated than riociguat-pretreated patients (Table 5). Of the six patients with serious hemoptysis, three were receiving concomitant anticoagulants, two were receiving a concomitant prostanoid, and one was receiving concomitant antiplatelet therapy.

The incidence of hypotension was low across all subgroups (Supplementary Table 5). There were no events of hemoptysis in patients receiving combination therapy with riociguat and a prostanoid, with or without an ERA.

3.6. Deaths and fatal SAEs

Of the 326 patients, 44 (13.5%) (21 riociguat-newly treated [14.6%] and 23 riociguat-pretreated [12.6%]) died or experienced an SAE with a fatal outcome with onset during the study. These SAEs began during the treatment phase in 40 patients (12.3%): 19 riociguat newly-treated patients (13.2%) and 21 riociguat-pretreated patients (11.5%). Fatal SAEs with post-treatment onset occurred in two riociguat-newly treated patients (1.4%) and two riociguat-pretreated patients (1.1%). The most common fatal SAEs overall were RV failure in 9 patients (2.7%); multiple organ dysfunction syndrome in 3 (0.9%); and respiratory failure, PAH, dyspnea, and sudden cardiac death, each in 2 patients (0.6%). In 10 patients (3.1%), the SAE was death (cause unknown). The death of one patient with PAH was considered related to riociguat by the investigator. This was a case of hemoptysis, which was complicated by concurrent hereditary hemorrhagic telangiectasia and atypical pneumonia.

Table 3
Baseline demographics and disease characteristics in riociguat-pretreated and riociguat-newly treated patients.

	Riociguat-pretreated[a] (n = 182)	Riociguat-newly treated[b] (n = 144)
Age, years	52.9 ± 15.7	55.4 ± 17.4
Age group, years, n (%)		
<65	138 (75.8)	98 (68.1)
65 to < 75	31 (17.0)	20 (13.9)
≥75	13 (7.1)	26 (18.1)
Female sex, n (%)	132 (72.5)	102 (70.8)
BMI, kg/m^2	27.9 ± 15.0	25.9 ± 5.3
BMI category, kg/m^2, n (%)		
<18.5	5 (2.7)	8 (5.6)
18.5 to < 25	78 (42.9)	59 (41.0)
25 to < 30	51 (28.0)	45 (31.3)
≥30	48 (26.4)	32 (22.2)
Smoking status, n (%)		
Never	127 (69.8)	91 (63.2)
Former	49 (26.9)	42 (29.2)
Current	6 (3.3)	11 (7.6)
Prevalent (disease duration ≥ 6 months), n (%)	170 (93.4)	84 (58.3)
Incident (disease duration < 6 months), n (%)	8 (4.4)	53 (36.8)
Duration status unknown, n (%)	4 (2.2)	7 (4.9)
Age at initial PH diagnosis, years	47.2 ± 16.5 (n = 178)	51.0 ± 18.0 (n = 138)
Median (IQR) PH disease duration, years	4.4 (1.8–7.4) (n = 178)	1.5 (0.2–5.7) (n = 138)
WHO FC, % (I/II/III/IV/unknown)	3.8/43.4/43.4/5.5/3.8	4.2/20.8/56.9/8.3/9.7
BNP, pg/mL, median (range)	128 (5.8–497) (n = 34)	362 (12–1305) (n = 23)
NT-proBNP, pg/mL, median (range)	333 (12–19 936) (n = 76)	590 (45–79 080) (n = 56)
6MWD, m	402 ± 130 (n = 161)	366 ± 132 (n = 121)
6MWD, n (%)		
<320 m[c]	40 (22.0)	36 (25.0)
≥320 m	121 (66.5)	85 (59.0)
<380 m[c]	60 (33.0)	62 (43.1)
≥380 m	101 (55.5)	59 (41.0)
Missing	21 (11.5)	23 (16.0)
EQ-5D VAS	59.0 ± 23.7 (n = 69)	61.6 ± 20.2 (n = 44)
Borg Dyspnea Index	4.1 ± 2.3 (n = 138)	4.1 ± 2.4 (n = 114)
mPAP, mmHg	50.6 ± 15.3 (n = 152)	53.1 ± 13.6 (n = 130)
PVR, dyn·s·cm^{-5}	757 ± 546 (n = 137)	894 ± 502 (n = 124)
PAWP, mmHg	10.8 ± 5.8 (n = 145)	9.9 ± 4.8 (n = 125)
Cardiac index, L/min/m^2	2.6 ± 1.5 (n = 132)	2.4 ± 0.7 (n = 113)
RAP, mmHg	9.7 ± 7.2 (n = 120)	8.7 ± 5.5 (n = 91)
SvO_2 (%)	65.0 ± 10.5 (n = 113)	62.8 ± 12.1 (n = 98)
Riociguat daily dose at initial study visit, mg		
Mean	7.0 ± 1.0	6.6 ± 1.5 (n = 140)
Median (range)	7.5 (1.5–7.5)	7.5 (1.5–7.5) (n = 140)
Riociguat median daily dose at initial study visit, mg, n (%)		
≤2.5	1 (0.5)	2 (1.4)
>2.5 to 4.5	11 (6.0)	21 (14.6)
>4.5 to 6	34 (18.7)	23 (16.0)
>6 to 7.5	136 (74.7)	94 (65.3)
Missing	0 (0.0)	4 (2.8)
PH-approved regimen at initial study visit, n (%)		
Riociguat monotherapy[d]	39 (21.4)	49 (34.0)
Riociguat combination therapy[e,f]	143 (78.6)	95 (66.0)
Riociguat + ERA	113 (62.1)	70 (48.6)
Riociguat + ambrisentan	26 (14.3)	9 (6.3)
Riociguat + bosentan	49 (26.9)	27 (18.8)
Riociguat + macitentan	38 (20.9)	34 (23.6)
Riociguat + prostanoid	9 (4.9)	3 (2.1)
Riociguat + inhaled epoprostenol	0 (0.0)	1 (0.7)
Riociguat + IV treprostinil	3 (1.7)	1 (0.7)
Riociguat + iloprost	6 (3.3)	1 (0.7)
Riociguat + ERA + prostanoid	21 (11.5)	22 (15.3)
Concomitant CCB, n (%)	9 (4.9)	13 (9.0)
Anticoagulation therapy, n (%)		
Oral anticoagulation	96 (52.7)	65 (45.1)
Vitamin K antagonist	69 (37.9)	42 (29.2)
Direct oral anticoagulant	18 (9.9)	19 (13.2)
Other oral anticoagulation[g]	10 (5.5)	2 (1.4)
Other anticoagulant[g]	4 (2.2)	3 (2.1)
Antiplatelet agents, n (%)	17 (9.3)	24 (16.7)
Comorbidity, n (%)		
At least one medical history finding	163 (89.6)	130 (90.3)
Arterial hypertension	60 (33.0)	55 (38.2)
Thyroid disease	38 (20.9)	42 (29.2)
Diabetes mellitus	26 (14.3)	24 (16.7)
Coronary heart disease	25 (13.7)	22 (15.3)

(*continued on next page*)

Table 3 (*continued*)

	Riociguat-pretreated[a] (n = 182)	Riociguat-newly treated[b] (n = 144)
Obstructive sleep apnea	19 (10.4)	12 (8.3)
Venous thromboembolism	14 (7.7)	11 (7.6)
Cancer	7 (3.8)	13 (9.0)
History of hemoptysis/lung bleeding	5 (2.7)	3 (2.1)
Other	142 (78.0)	108 (75.0)

6MWD, 6-min walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; EQ-5D VAS, EuroQoL 5-dimensional Visual Analog Score; ERA, endothelin receptor antagonist; IQR, interquartile range; IV, intravenous; mPAP, mean pulmonary artery pressure; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SD, standard deviation; SvO_2, saturated venous oxygen; WHO FC, World Health Organization functional class.

Data are mean ± SD unless otherwise stated.

[a] Receiving riociguat for ≥3 months before entry (n = 182 unless otherwise stated).

[b] Receiving riociguat for <3 months before entry (n = 144 unless otherwise stated).

[c] Thresholds chosen (380 m prespecified) based on available (6MWD) cohort data at the time indicating good or poor prognosis [16,17].

[d] Patients receiving riociguat but no ERA or prostanoid.

[e] Patients receiving riociguat + ERA, prostanoid, or both.

[f] No patient received concomitant PDE5i during the study.

[g] As indicated by the investigator on the CRF.

Estimated survival rates in the total PAH population at 1, 2, and 3 years were 94.2% (95% CI, 90.9–96.3%), 82.2% (95% CI, 75.5–87.2%), and 71.0% (95% CI, 60.8–79.0%), respectively. Kaplan−Meier survival curves for riociguat-newly treated and riociguat-pretreated patients with PAH are shown in Fig. 4.

In the post hoc analysis assessing patients according to disease duration, death during the treatment period was numerically more common in prevalent PAH patients (34 patients; 13.4%) than in incident PAH patients (3 patients; 4.9%). Two patients in each group (0.8% of prevalent patients and 3.3% of incident patients) died during the 30-day safety follow-up.

3.7. Other results

3.7.1. Efficacy assessments

Results for indicators of efficacy (6MWD, Borg Dyspnea Index, EQ-5D VAS, hemodynamic measurements, and biomarkers) had many missing data and varied greatly between patients. Moreover, selection bias for repeat efficacy assessments could confound the results. These results are therefore not shown or discussed here.

4. Discussion

4.1. Safety findings

EXPERT provided data on the safety and tolerability of riociguat in more than 300 patients with PAH in real-world clinical practice. The types of AEs observed were consistent with those reported in PATENT-1 [8] and PATENT-2 [10,11], with no new safety signals identified. The most common events (e.g., peripheral edema/edema, dizziness, hypotension, RV failure/cardiac failure, dyspnea) were consistent with symptoms of the underlying disease or with vasodilatation by riociguat. Concomitant anticoagulants, antiplatelet therapy, or prostanoids (which have antiplatelet actions) may have contributed to bleeding AEs in some patients. The exposure-adjusted rates of hypotension and hemoptysis/-pulmonary hemorrhage were lower than those reported in PATENT-2 (6.2 and 5.5 events, respectively, per 100 patient-years) [10]. Most patients were receiving combination therapy, mainly with ERAs. In patients receiving riociguat as part of a combination regimen, the overall incidence of AEs was slightly higher than in patients receiving monotherapy. AEs considered drug-related by the investigator were more common with riociguat monotherapy than with combination

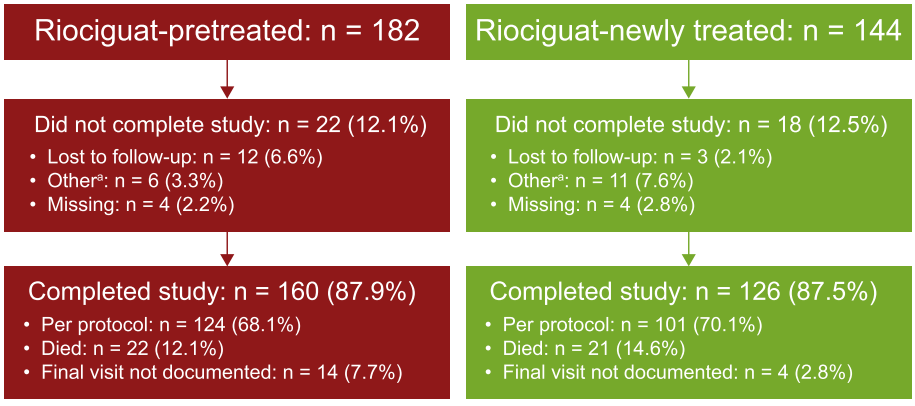

Fig. 3. Disposition of riociguat-pretreated and riociguat-newly treated patients with PAH.
Chart shows primary reason for discontinuation.
[a]Other reasons for not completing the study are listed in Supplementary Table 1.

Table 4
Safety summary in riociguat-pretreated and riociguat-newly treated patients.

	Riociguat-pretreated[a] (n = 182)	Riociguat-newly treated[b] (n = 144)
Any AE	122 (67.0)	107 (74.3)
Most common AEs[c]		
Dizziness	18 (9.9)	20 (13.9)
Diarrhea	19 (10.4)	9 (6.3)
Peripheral edema/edema	19 (10.4)[d]	16 (11.1)[e]
Cough	15 (8.2)	10 (6.9)
RV failure/cardiac failure	19 (10.4)[f]	16 (11.1)[g]
Dyspnea	13 (7.1)	13 (9.0)
Nasopharyngitis	13 (7.1)	6 (4.2)
Pneumonia	10 (5.5)	12 (8.3)
Fatigue	7 (3.8)	8 (5.6)
Hypokalemia	6 (3.3)	8 (5.6)
Nausea	6 (3.3)	8 (5.6)
Chest discomfort	5 (2.7)	8 (5.6)
Hypotension	2 (1.1)	11 (7.6)
Any drug-related AE[h]	13 (7.1)	36 (25.0)
Discontinuation due to AE	4 (2.2)	20 (13.9)
Any SAE	74 (40.7)	78 (54.2)
Most common SAEs[i]		
RV failure/cardiac failure	19 (10.4)[j]	14 (9.7)[k]
Pneumonia	9 (4.9)	11 (7.6)
PAH[l]	7 (3.8)	4 (2.8)
PH[l]	6 (3.3)	4 (2.8)
Death (cause unknown)[m]	6 (3.3)	3 (2.1)
Dyspnea	5 (2.7)	8 (5.6)
Syncope	5 (2.7)	6 (4.2)
Respiratory tract infection	5 (2.7)	4 (2.8)
Acute kidney injury	5 (2.7)	3 (2.1)
Anemia	4 (2.2)	1 (0.7)
Ascites	4 (2.2)	0 (0.0)
Atrial fibrillation	3 (1.6)	5 (3.5)
Hemoptysis	3 (1.6)	3 (2.1)
Hypotension	0 (0.0)	5 (3.5)
Hypoxia	0 (0.0)	3 (2.1)
Lung infection	0 (0.0)	3 (2.1)
Oxygen therapy	0 (0.0)	3 (2.1)
Any drug-related SAE[h]	5 (2.7)	18 (12.5)
Discontinuation due to SAE	4 (2.2)	17 (11.8)

All data are n (%). AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RV, right ventricular; SAE, serious adverse event.
Note. Patients with peripheral edema/edema, or RV failure/cardiac failure, could have both events.
[a] Receiving riociguat for ≥3 months before entry. Median (range) duration of observation and riociguat treatment (days): 472.5 (0.0–1373.0); 467.0 (0.0–1373.0).
[b] Receiving riociguat for <3 months before entry. Median (range) duration of observation and riociguat treatment (days): 472.5 (0.0–1381.0); 464.0 (0.0–1381.0).
[c] Preferred-term AEs reported in ≥5% of patients in either group.
[d] Including edema in 3 patients (1.6%) and peripheral edema in 16 patients (8.8%).
[e] Including edema in 10 patients (6.9%) and peripheral edema in 6 patients (4.2%).
[f] Including RV failure in 15 patients (8.2%) and cardiac failure in 4 patients (2.2%).
[g] Including RV failure in 10 patients (6.9%) and cardiac failure in 6 patients (4.2%).
[h] Investigator's causality assessment.
[i] Preferred-term SAEs reported in ≥2% of patients in either group.
[j] Including RV failure in 15 patients (8.2%) and cardiac failure in 4 patients (2.2%).
[k] Including RV failure in 10 patients (6.9%) and cardiac failure in 4 patients (2.8%).
[l] Preferred term for worsening of condition.
[m] Cases with MedDRA preferred term, "Death" under MedDRA system organ class, "General Disorders and Administration Site Condition" with adverse event lowest level term, "Unknown cause of death".

Table 5
AEs and SAEs of special interest.

	All PAH (n = 326)[a]	Riociguat-pretreated[b] (n = 182)	Riociguat-newly treated[c] (n = 144)
Absolute AE rates, n (%)			
Hypotension	13 (4.0)	2 (1.1)	11 (7.6)
Hemoptysis	8 (2.5)	4 (2.2)	4 (2.8)
Exposure-adjusted AE rates (95% CI)[d]			
Hypotension	2.7 (1.5–4.5)	0.7 (0.1–2.2)	5.8 (3.0–9.9)
Hemoptysis	2.5 (1.4–4.2)	2.1 (0.8–4.3)	3.2 (1.3–6.4)
Absolute SAE rates, n (%)			
Hypotension	5 (1.5)	0 (0.0)	5 (3.5)
Hemoptysis	6 (1.8)	3 (1.6)	3 (2.1)
Exposure-adjusted SAE rates (95% CI)[d]			
Hypotension	1.1 (0.4–2.3)	0 (0.0–0.0)	2.6 (0.9–5.7)
Hemoptysis	1.7 (0.8–3.1)	1.4 (0.4–3.3)	2.1 (0.7–4.9)

AE, adverse event; CI, confidence interval; PAH, pulmonary arterial hypertension; SAE, serious adverse event.
Note. Pulmonary hemorrhage was not reported in any patient.
[a] Median (range) duration of observation and riociguat treatment (days): 472.5 (0.0–1381.0); 467.0 (0.0–1381.0).
[b] Receiving riociguat for ≥3 months before entry. Median (range) duration of observation and riociguat treatment (days): 472.5 (0.0–1373.0); 467.0 (0.0–1373.0).
[c] Receiving riociguat for <3 months before entry. Median (range) duration of observation and riociguat treatment (days): 472.5 (0.0–1381.0); 464.0 (0.0–1381.0).
[d] Rates per 100 patient-years, calculated by the number of events divided by (total drug exposure in years/100).

therapy, which may be because it is easier to link an AE to treatment if the patient is receiving only one drug. These data should be interpreted with caution as they are descriptive, they are not adjusted for differences between the combination and monotherapy groups, they refer to treatment at baseline, and the number of patients receiving riociguat plus a prostanoid as dual therapy was very small. Overall, however, the results indicate the safety of riociguat as monotherapy and in combination regimens (co-administration with PDE5i is contraindicated and was not observed in EXPERT).

Clinical experience with riociguat shows an increased frequency of some AEs such as hypotension, dizziness, and edema during dose adjustment [6,7]. These effects, described in the reference safety information for the drug, have been attributed to the vasodilatory properties of riociguat [6]. In EXPERT, as expected, numerically more riociguat-newly treated patients than riociguat-pretreated patients experienced AEs and discontinued treatment because of AEs or SAEs. These observations may be partly explained by a worse disease state, as indicated by baseline 6MWD and WHO FC, but also partly by more frequent measurements (e.g., of blood pressure) in the newly treated group. For riociguat-pretreated patients, bias may be introduced, because those who had to discontinue the drug because of AEs, or who died, could not be documented in the study.

Several registries, including the French PAH registry [18] and REVEAL [19], have reported better survival in prevalent than in incident PAH cohorts. It has been suggested that prevalent cohorts are enriched with patients with better RV function or a better response to therapy or that many higher-risk patients do not survive long enough to be enrolled as previously diagnosed patients [18–20]. In our post hoc analysis, however, rates of AEs and SAEs were similar between prevalent and incident patients, indicating that the higher proportion of incident patients in the riociguat-newly treated group than in the riociguat-pretreated group did not disadvantage them in terms of safety. There is no explanation for the greater number of deaths in prevalent patients than incident patients but it may be related to the longer PAH disease duration in the prevalent group.

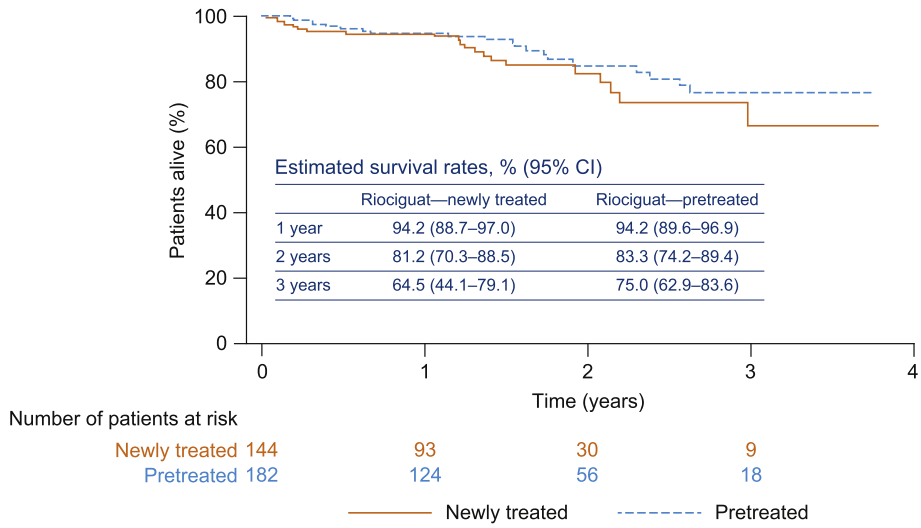

Fig. 4. Kaplan–Meier survival curves for riociguat-pretreated and riociguat-newly treated patients. CI, confidence interval.

4.2. Comparison with other studies

The demographics and disease characteristics of patients with PAH in EXPERT were similar to those seen in the REVEAL registry overall [21] and the incident group in REVEAL [19]. Patients with PAH in EXPERT were approximately 4 years older than in the French National Registry [22]. The association of EXPERT with COMPERA, in which patients are older than in other registries [23], may have encouraged the enrollment of older patients.

The estimated 1-year survival in patients with PAH in EXPERT was comparable to REVEAL (91.0%) [24], the Giessen registry (88.2%) [25], the VOLibris post-authorization registry of ambrisentan (91%) [26], a large retrospective analysis of US veterans (90.2%) [27], and a low-risk population identified in a COMPERA analysis (97.2%) [23]. Survival at 3 years was also within the range reported elsewhere [25].

Registries provide important information about the safety of drugs in clinical practice, and thus supplement information gained from selected populations under the closely controlled conditions of clinical trials. They may also detect previously unsuspected safety signals. Limitations inherent in registries including confounding, lack of randomization, missing values, and the hazards of generalizing data from the registry population to other populations [28], also apply to EXPERT. In addition, EXPERT was designed to collect safety information on riociguat; it was not designed to provide data on the long-term efficacy of this drug. The power analysis for EXPERT was done for the total population. The subgroup analysis of PAH patients (n = 326) does not necessarily meet the power criteria, and the lower number of patients in subgroup analyses may result in an under-detection of AEs.

Strengths of EXPERT include the relatively long observation time (median: 473 days) and the large proportion of patients completing the study (88%).

5. Conclusion

Final data from the EXPERT registry showed that in patients with PAH, the long-term safety of riociguat in routine practice was consistent with clinical trials, with no new safety concerns identified.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Prof Marius M. Hoeper reports personal fees from Bayer AG, during the conduct of the study; personal fees from Actelion, personal fees from Acceleron, personal fees from MSD, personal fees from Jansen, personal fees from Pfizer, outside the submitted work. Dr Hans Klose reports speaker and consultancy fees from Actelion, Bayer AG, GSK, Novartis, Pfizer, and United Therapeutics and research support from Actelion, Bayer AG, GSK, Pfizer, and MSD. Dr Michael Halank reports personal fees and non-financial support from Actelion, AstraZeneca, Bayer AG, Berlin-Chemie, GSK, OMT, MSD, and Novartis. Dr George Giannakoulas reports speaker and consultancy fees from Actelion, Bayer AG, ELPEN Pharmaceuticals, GSK, Pfizer, Lilly, and United Therapeutics, and research support from GSK, ELPEN Pharmaceuticals, and Galenica. 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Appendix A. Supplementary data

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