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Original Research

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

Hossein-Ardeschir Ghofrani [a,b,*], Miguel-Angel Gomez Sanchez [c,d], Marc Humbert [e], David Pittrow [f], Gérald Simonneau [g], Henning Gall [a,b], Ekkehard Grünig [h], Hans Klose [i], Michael Halank [j], David Langleben [k], Repke J. Snijder [l], Pilar Escribano Subias [m,n], Lisa M. Mielniczuk [o], Tobias J. Lange [p], Jean-Luc Vachiéry [q], Hubert Wirtz [r], Douglas S. Helmersen [s], Iraklis Tsangaris [t], Joan A. Barberá [u,v], Joanna Pepke-Zaba [w], Anco Boonstra [x], Stephan Rosenkranz [y], Silvia Ulrich [z], Regina Steringer-Mascherbauer [aa], Marion Delcroix [ab], Pavel Jansa [ac], Iveta Šimková [ad], George Giannakoulas [ae], Jens Klotsche [af], Evgenia Williams [ag], Christian Meier [ag], Marius M. Hoeper [ah], NEW COLLABORATORS LIST

[a] *University of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany*
[b] *Member of the German Center for Lung Research (DZL), Giessen, Germany*
[c] *Respiratory Department, Ramón y Cajal University Hospital (IRYCIS), Madrid, Spain*
[d] *Biomedical Research Networking Centre on Respiratory Diseases (CIBERES), Spain*
[e] *Université Paris-Saclay, Inserm U999, Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, France*
[f] *Institute for Clinical Pharmacology, Technical University, Dresden, Germany*
[g] *Université Paris-Sud, Le Kremlin-Bicêtre, Service de Pneumologie, Centre de Référence de l'Hypertension Pulmonaire Sévère, DHU Thorax Innovation, Hôpital Bicêtre, Le Kremlin-Bicêtre, Paris, France*
[h] *Centre for Pulmonary Hypertension, Thoraxclinic at Heidelberg University Hospital, Heidelberg, Germany*
[i] *Department of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[j] *Medical Clinic I, Department of Pneumology, University Hospital Carl Gustav Carus, Dresden, Germany*
[k] *Center for Pulmonary Vascular Disease, Jewish General Hospital, McGill University, Montreal, Quebec, Canada*
[l] *Department of Pulmonology, St Antonius Ziekenhuis, Nieuwegein, the Netherlands*
[m] *Department of Cardiology, Hospital 12 de Octubre, Madrid, Spain*
[n] *CIBER-CV (CIBER of Cardiovascular Disease), Hospital 12 de Octubre, Madrid, Spain*
[o] *Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, Ottawa, Ontario, Canada*
[p] *Department of Internal Medicine II, Division of Pneumology, University Medical Center, Regensburg, Germany*
[q] *Département de Cardiologie, Cliniques Universitaires de Bruxelles, Hôpital Erasme, Brussels, Belgium*
[r] *Department of Respiratory Medicine, University of Leipzig, Leipzig, Germany*
[s] *Alberta Health Services, University of Calgary, Calgary, Alberta, Canada*
[t] *Second Department of Critical Care, University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece*
[u] *Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain*
[v] *Biomedical Research Networking Center on Respiratory Diseases (CIBERES), Madrid, Spain*
[w] *Pulmonary Vascular Disease Unit, Royal Papworth Hospital, Cambridge, UK*
[x] *VU Medisch Centrum, Amsterdam, the Netherlands*
[y] *Department III of Internal Medicine and Cologne Cardiovascular Research Center (CCRC), Cologne University Heart Center, Cologne, Germany*
[z] *Clinic of Pulmonology, University Hospital Zurich, Zurich, Switzerland*
[aa] *Servicestelle für klinische Studien, Krankenhaus der Elisabethinen Linz GmbH, Linz, Austria*
[ab] *Department of Respiratory Diseases, University Hospitals of Leuven, and Respiratory Division, Department CHROMETA, KU Leuven – University of Leuven, Leuven, Belgium*
[ac] *2nd Department of Medicine, Department of Cardiovascular Medicine, Charles University in Prague, Prague, Czech Republic*
[ad] *Department of Cardiology and Angiology, Faculty of Medicine, Slovak Medical University & National Institute of Cardiovascular Diseases, Bratislava, Slovak Republic*
[ae] *Department of Cardiology I, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[af] *German Rheumatism Research Center Berlin, Leibniz Institute, Berlin, Germany*
[ag] *Bayer AG, Global Development, Global Medical Affairs, Berlin, Germany*
[ah] *Department of Respiratory Medicine and the German Center for Lung Research, Hannover Medical School, Hannover, Germany*

* Corresponding author. University of Giessen and Marburg Lung Center (UGMLC), Giessen, 35392, Germany.
E-mail address: Ardeschir.Ghofrani@innere.med.uni-giessen.de (H.-A. Ghofrani).

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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 (CTEPH) 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 and collated via case report forms.

Results: In total, 956 patients with CTEPH were included in the analysis. The most common AEs in these patients were peripheral edema/edema (11.7%), dizziness (7.5%), right ventricular (RV)/cardiac failure (7.7%), and pneumonia (5.0%). The most common SAEs were RV/cardiac failure (7.4%), pneumonia (4.1%), dyspnea (3.6%), and syncope (2.5%). Exposure-adjusted rates of hemoptysis/pulmonary hemorrhage and hypotension were low and comparable to those in the long-term extension study of riociguat (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial [CHEST-2]).

Conclusion: Data from EXPERT show that in patients with CTEPH, the safety of riociguat in routine practice was consistent with the known safety profile of the drug, and no new safety concerns were identified.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially fatal condition characterized by obstruction of the pulmonary vasculature by residual organized thrombi resulting in increased pulmonary vascular resistance (PVR), progressive vascular remodeling and pulmonary hypertension (PH), and subsequently right ventricular (RV) failure [1–5].

The treatment of choice in CTEPH is pulmonary endarterectomy (PEA), which potentially normalizes hemodynamics [5–8]. Up to 40% of patients are inoperable, however, and up to 51% exhibit persistent or recurrent CTEPH after PEA [6–14].

Riociguat is a first-in-class soluble guanylate cyclase stimulator recommended in European Respiratory Society/European Society of Cardiology guidelines for the treatment of patients with inoperable CTEPH or persistent/recurrent CTEPH after surgery [1]. Its efficacy and tolerability have been demonstrated in clinical trials [15,16]. Agents that have been approved for pulmonary arterial hypertension (PAH) include prostacyclin analogs, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 inhibitors (PDE5i). With the exception of treprostinil in selected patients, these are not licensed for use in the treatment of patients with CTEPH, but can be administered off-label. Balloon pulmonary angioplasty (BPA) is a potentially effective option for selected inoperable patients [1,17].

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 in patients treated with riociguat in 28 countries. The design is described in detail elsewhere [18]. 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 use existing registries. EXPERT was conducted in accordance with good pharmacovigilance practices and was not requested, but was accepted, by the European Medicines Agency for the collection of additional long-term post-approval data on riociguat.

Patients were followed for 1–4 years from enrollment (including post-treatment safety follow-up) during a recruitment period of 3 years or until 30 days after stopping riociguat treatment. Data—including patient demographics, disease characteristics, riociguat dosing, hemodynamic parameters, changes in treatment, biomarkers, laboratory variables, adverse events (AEs) and serious adverse events (SAEs)—were collected at baseline and during routine clinical follow-up visits approximately every 3–6 months. Data were collected using a case report form (CRF) based on the COMPERA CRF, extended to obtain riociguat safety data.

2.2. Patients

Patients who started treatment or were already being treated with riociguat were eligible for inclusion. 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 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. Safety assessments

The primary safety outcomes were AEs and SAEs, coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and System Organ Classes version 21.0. Secondary safety outcomes included AEs and SAEs of special interest (hypotension and hemoptysis/pulmonary hemorrhage). This report focuses on AEs and SAEs occurring during the treatment phase (onset date $\leq$ 2 days after the most recent dose of riociguat). 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. AEs and SAEs were classified as drug-related according to the investigator's judgment. 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 30-day safety follow-up).

2.4. Statistical methods and populations analyzed

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 ± standard deviation [SD], median, and minimum–maximum range). 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. Summary statistics and changes from baseline were calculated for 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, and biomarkers. This paper describes the results in patients with CTEPH. Results in patients with PAH are described separately [18].

3. Results

3.1. Patient disposition

The evaluable population with CTEPH consisted of 956 patients of whom 537 (56.2%) were riociguat-pretreated and 419 (43.8%) were riociguat-newly treated. Approximately 86% of patients overall completed the study (Fig. 1).

3.2. Demographics and baseline characteristics

The mean age of the patients was 66.3 ± 13.7 years; 570 patients (59.6%) were women. CTEPH was prevalent in 713 patients (74.6%), incident in 197 (20.6%), and unknown in 46 (4.8%). At baseline, riociguat was administered in combination with other PH-approved therapy in 198 patients (20.7%): with ERAs in 170 (17.8% [bosentan, 7.0%; macitentan, 7.0%; and ambrisentan, 3.8%]), prostanoids in 9 (0.9% [iloprost, 0.6%; intravenous treprostinil, 0.2%; and intravenous epoprostenol, 0.1%]), and both an ERA and prostanoid in 19 (2.0%). No patient received concomitant PDE5i. At Visit 6 (month 33−< 39), 27.9% of patients were receiving combination therapy. In total, 901 patients (94.2%) had at least one comorbidity. Other baseline demographics are shown in Table 1. The operability status of the patients is shown in Fig. 2.

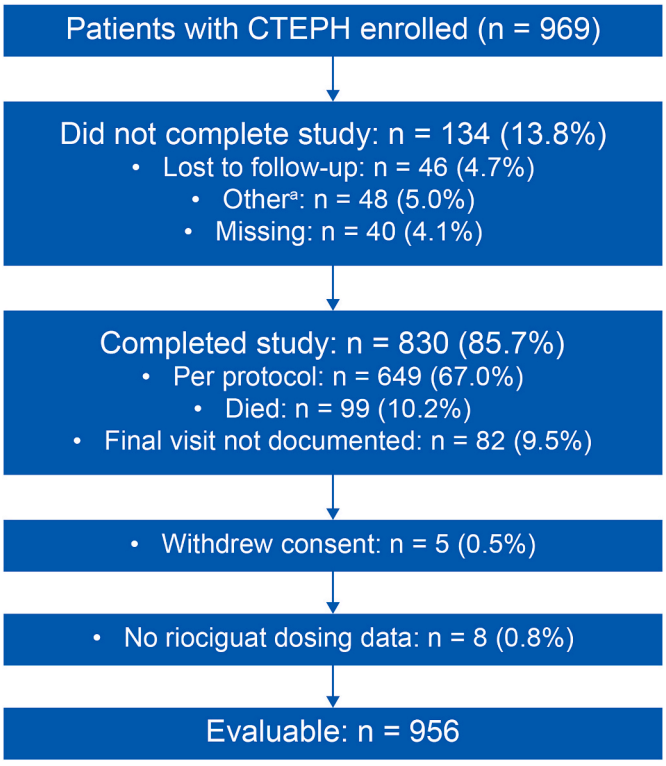

Fig. 1. Patient disposition.
CTEPH, chronic thromboembolic pulmonary hypertension. The numbers and percentages refer to the total CTEPH population enrolled (n = 969). Chart shows primary reason for not completing per protocol.
[a]Other reasons for discontinuation are shown in Supplementary Table 1.

3.3. Riociguat safety

3.3.1. Total CTEPH population

In the total population with CTEPH, the median (range) duration of observation and riociguat treatment was 504.0 (0.0–1367.0) days and 493.5 (0.0–1367.0) days, respectively. In total, 615 patients (64.3%) experienced AEs and 365 (38.2%) experienced SAEs. These events were considered drug-related by the investigator in 148 (15.5%) and 34 (3.6%) patients, respectively. The most common AEs and SAEs are shown in Table 2. Discontinuation due to AEs and SAEs occurred in 55 patients (5.8%) and 38 patients (4.0%), respectively. The most common AEs or SAEs leading to discontinuation are shown in Supplementary Table 2. Safety data for patients according to use of riociguat as monotherapy or in combination with other PAH-approved drugs are shown in Supplementary Table 3. Rates of AEs and SAEs (68.2–88.9% and 44.1–66.7%, respectively) were numerically higher with prostanoid-containing regimens (78.9–88.9% and 57.9–66.7%, respectively) than with riociguat monotherapy or riociguat + ERA (62.8–68.2% and 36.0–44.1%, respectively), but the numbers of patients receiving prostanoids were small.

Hemorrhages were reported in 110 patients (11.5%) and serious hemorrhages in 57 patients (6.0%). These events were considered by the investigator to be related to riociguat in nine (0.9%) and four patients (0.4%), respectively. Three patients (0.3%) discontinued riociguat as a result of a hemorrhage. The most frequently occurring hemorrhages were epistaxis in 30 patients (3.1%) and hemoptysis in 26 patients (2.7%). The most common serious hemorrhages were hemoptysis in 16 patients (1.7%) and gastrointestinal hemorrhage in five patients (0.5%). Of all patients who experienced a hemorrhage, 78 were recorded as receiving a vitamin K antagonist (VKA) and 24 as receiving non-VKA oral anticoagulants (NOACs). Hemoptysis and pulmonary hemorrhage were considered AEs of special interest and are discussed further below.

3.3.2. Safety in prevalent vs. incident patients

A post hoc analysis compared prevalent patients (disease duration ≥ 6 months) (n = 713) with incident patients (diagnosed within < 6 months of enrollment) (n = 197) according to disease duration data available at baseline. Disease characteristics, including 6MWD and WHO FC, indicated a more severe disease status in incident patients compared with prevalent patients (data not shown). Median disease duration was 1.8 (range, 0.0–6.0) months in incident patients and 3.2 (range, 0.5–39.7) years in prevalent patients. AEs were reported in 471 prevalent patients (66.1%) and 119 incident patients (60.4%), and SAEs in 276 (38.7%) and 73 (37.1%) prevalent and incident patients, respectively.

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

Compared with riociguat-pretreated patients, riociguat-newly treated patients had a numerically shorter disease duration, shorter 6MWD, a higher proportion of WHO FC III/IV disease, and a greater proportion of incident disease (Table 3). More than 90% of patients in both groups had at least one comorbidity. Approximately 89% of riociguat-pretreated patients and 83% of riociguat-newly treated patients completed the study (Fig. 3). Of the riociguat-newly treated patients, 72 (17.2%) had switched from previous PAH-approved therapy: 65 (15.5%) from PDE5i, 5 (1.2%) from a prostanoid, and 12 (2.9%) from an ERA (some patients switched from more than one prior therapy).

AEs were reported in 270 riociguat-newly treated patients (64.4%) and 345 riociguat-pretreated patients (64.2%). SAEs were reported in 166 riociguat-newly treated patients (39.6%) and 199 riociguat-pretreated

Table 1
Baseline demographics and disease characteristics in the total CTEPH population (n = 956).

Characteristic	Mean ± SD or n (%)	Characteristic	Mean ± SD or n (%)
Age, years	66.3 ± 13.7	Riociguat daily dose at initial study visit, mg	
Age group, years		Mean	6.9 ± 1.4 (n = 934)
< 65	366 (38.3)	Median (range)	7.5 (1.5–7.5) (n = 934)
65 to < 75	260 (27.2)		
≥ 75	330 (34.5)		
BMI, kg/m^2	28.6 ± 15.2	Riociguat median daily dose at initial study visit, mg	
BMI category, kg/m^2		≤ 2.5	13 (1.4)
< 18.5	24 (2.5)	> 2.5 to 4.5	108 (11.3)
18.5 to < 25	290 (30.3)	> 4.5 to 6	90 (9.4)
25 to < 30	348 (36.4)	> 6 to 7.5	723 (75.6)
≥ 30	294 (30.8)	Missing	22 (2.3)
Smoking status		Concomitant CCB	22 (2.3)
Never	602 (63.0)		
Former	314 (32.8)	Concomitant anticoagulation therapy	
Current	40 (4.2)	Oral anticoagulation	861 (90.1)
Age at initial PH diagnosis, years	62.7 ± 14.5	Vitamin K antagonist	506 (52.9)
Median (IQR) disease duration, years	2.1 (0.7–4.9)	Direct oral anticoagulant	190 (19.9)
		Other oral anticoagulation[b]	159 (16.6)
		Other anticoagulant[b]	66 (6.9)
		Concomitant antiplatelet agents	44 (4.6)
WHO FC, % (I/II/III/IV/unknown)	4.0/38.2/50.1/3.0/4.7	Comorbidity	
BNP, pg/mL (median, range)	131 (5–5844) (n = 148)	At least one medical history finding	901 (94.2)
NT-proBNP, pg/mL (median, range)	602 (16–177 759) (n = 540)	Arterial hypertension	445 (46.5)
6MWD, m	365 ± 128	Venous thromboembolism	431 (45.1)
6MWD		Thyroid disease	183 (19.1)
< 320 m[a]	290 (30.3)	Diabetes mellitus	123 (12.9)
≥ 320 m	521 (54.5)	Cancer	123 (12.9)
< 380 m	421 (44.0)	Coronary heart disease	122 (12.8)
≥ 380 m[a]	390 (40.8)	Obstructive sleep apnea	99 (10.4)
Missing	145 (15.2)	History of hemoptysis/lung bleeding	37 (3.9)
EQ-5D VAS	62.3 ± 20.6 (n = 229)	Other	759 (79.4)
Borg Dyspnea Index	3.8 ± 2.2 (n = 701)		
mPAP, mmHg	43.0 ± 11.5 (n = 850)		
PVR, dyn·s·cm^{-5}	652 ± 502 (n = 767)		
PAWP, mmHg	11.1 ± 5.0 (n = 809)		
Cardiac index, L/min/m^2	2.8 ± 4.4 (n = 756)		
RAP, mmHg	9.0 ± 5.6 (n = 710)		
SvO_2, %	63.7 ± 9.2 (n = 613)		

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CTEPH, chronic thromboembolic pulmonary hypertension; 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; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; 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 (n = 956) unless otherwise stated.
[a] Thresholds chosen (380 m prespecified) based on available (6MWD) cohort data at the time indicating good or poor prognosis in PAH.
[b] As indicated by the investigator on the CRF.

patients (37.1%). 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). The types of AEs and SAEs were generally similar between the two groups. The most common AEs or SAEs leading to discontinuation are shown in Supplementary Table 4. Safety results in switched patients were generally similar to those in non-switched patients (data not shown). In riociguat-pretreated and riociguat-newly treated patients, AEs and SAEs were more frequent with combination therapy than with monotherapy (Supplementary Table 5).

3.4. AEs and SAEs of special interest

In general, AEs and SAEs of special interest were infrequent (Table 5). All of the 16 patients with serious hemoptysis/pulmonary hemorrhage overall were recorded as receiving concomitant anticoagulants, three as receiving concomitant antiplatelet therapy, and one as receiving a concomitant prostanoid. The incidence of hypotension was low across all subgroups (Supplementary Table 6).

3.5. AEs associated with PEA or BPA

In total, 47 patients (4.9%) underwent PEA (one operation in 44 patients [4.6%] and two operations in three patients [0.3%]). Within 10 days after PEA, nine of these patients (19.1%) had an AE, six (12.8%) had an SAE, and one (2.1%) had an AE-related death. No episode of hemoptysis was reported within 10 days following PEA. Also, 89 patients (9.3%) underwent BPA (mean: 2.1 ± 1.4 sessions; median: 2; range: 1–8) during the study. Within 10 days after BPA, six of these patients (6.7%) had an AE and six (6.7%) had

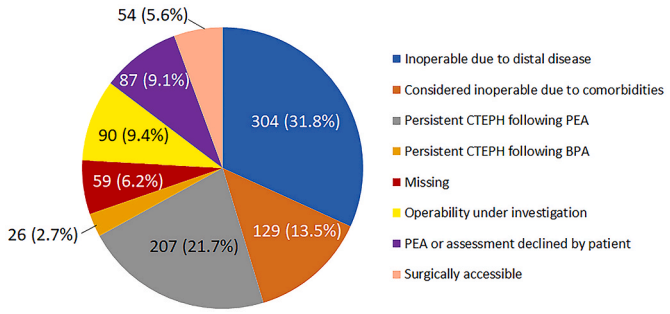

Fig. 2. Operability status.
BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy. Persistent CTEPH after PEA or BPA were determined by the investigator.

an SAE. No AE-related deaths were reported. The AEs included hemoptysis in two patients. Both events resolved, and neither was considered related to riociguat. None of the AEs reported within 10 days after PEA or BPA was considered related to riociguat.

3.6. Efficacy assessments

Results for indicators of efficacy (6MWD, Borg Dyspnea Index, EQ-5D VAS, hemodynamic measurements, and biomarkers) have not been the focus of this non-interventional study; many data were missing, and values varied greatly between patients. Selection bias for repeat efficacy assessments could confound the results. These results are therefore not shown or discussed here.

3.7. Deaths and fatal SAEs

Of the 956 patients with CTEPH, 101 (10.6%) (44 riociguat-newly treated patients [10.5%] and 57 riociguat-pretreated patients [10.6%]) died or experienced an SAE with a fatal outcome with onset during the study. These SAEs began during the treatment phase in 93 patients (9.7%); 38 riociguat-newly treated patients (9.1%) and 55 riociguat-pretreated patients (10.2%). Fatal SAEs with post-treatment onset occurred in six riociguat-newly treated patients (1.4%) and two riociguat-pretreated patients (0.4%). The most common fatal SAEs in the total CTEPH population were RV failure/cardiac failure in 27 patients (2.8%), followed by cardiac arrest, pneumonia, sepsis, and hemoptysis, each in three patients (0.3%). In 19 patients (2.0%), the SAE was listed as death (cause unknown). Two deaths were considered related to riociguat by the investigator. In one case the cause of death was hemoptysis, which occurred more than 2 years after therapy was initiated in a patient receiving concurrent anticoagulant medication. The other case was death from RV failure/cardiac failure, which occurred 10 days after the last dose of riociguat and was attributed to lack of efficacy of riociguat rather than an AE of the drug.

Table 2
Most common AEs and SAEs in the total CTEPH population (n = 956).

AEs[a]	n (%)
Peripheral edema/edema	112 (11.7)[b]
Dyspnea	81 (8.5)
RV failure/cardiac failure	74 (7.7)[c]
Dizziness	72 (7.5)
Pneumonia	48 (5.0)
SAEs[d]	
RV failure/cardiac failure	71 (7.4)[e]
Pneumonia	39 (4.1)
Dyspnea	34 (3.6)
Syncope	24 (2.5)
PH[f]	22 (2.3)

AE, adverse event; CTEPH, chronic thromboembolic pulmonary 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] Preferred-term AEs reported in ≥ 5% of patients.
[b] Including peripheral edema in 73 patients (7.6%) and edema in 42 patients (4.4%).
[c] Including RV failure in 61 patients (6.4%) and cardiac failure in 16 patients (1.7%).
[d] Preferred-term SAEs reported in ≥ 2% of patients.
[e] Including RV failure in 59 patients (6.2%) and cardiac failure in 15 patients (1.6%).
[f] Preferred term for worsening of the condition.

Estimated survival rates in the total CTEPH population at 1, 2, and 3 years were 94.7% (95% CI, 92.9–96.0%), 85.7% (95% CI, 82.4–88.4%), and 79.3% (95% CI, 74.0–83.6%), respectively. Kaplan–Meier survival curves for riociguat-newly treated and riociguat-pretreated patients are shown in Fig. 4.

In the post hoc analysis assessing patients according to disease duration, death during the treatment period occurred in 77 prevalent patients (10.8%) and 14 incident patients (7.1%). Four prevalent patients (0.6%) and four incident patients (2.0%) died during the 30-day safety follow-up.

4. Discussion

4.1. Safety findings

EXPERT provided data on the safety and tolerability of riociguat in more than 950 patients with CTEPH in real-world clinical practice. The types of AEs observed were consistent with those reported in Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial-1 (CHEST-1) [15], CHEST-2 [16,19], and the CTEPH Early Access Study [20], with no new safety signals identified. The most common events (e.g., peripheral edema/edema, dizziness, and dyspnea) were consistent with symptoms of the underlying disease or with vasodilatation by riociguat. Although the numbers of patients undergoing BPA or PEA were small, there was no evidence of an increased risk of drug-related events shortly after these procedures. The exposure-adjusted rate of hypotension (2.7 events per 100 patient-years) was lower than that reported in CHEST-2 (4.0 events per 100 patient-years) [19]. The rates of hemoptysis/pulmonary hemorrhage were similar (2.2 and 2.8 events per 100 patient-years in EXPERT and CHEST-2 [19], respectively). Most patients were receiving anticoagulants as required by CTEPH treatment guidelines: these may have contributed to the bleeding AEs. A separate publication comparing hemorrhagic and thrombotic/embolic events in patients receiving VKAs or NOACs at baseline is in preparation. In patients receiving riociguat as part of a combination regimen, the incidences of AEs and SAEs were higher than in patients receiving monotherapy. 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 numbers of patients receiving prostanoids were small. Clinical experience with riociguat shows an increased frequency of some AEs such as hypotension, dizziness, and edema during dose adjustment [21,22]. These effects, described in the reference safety information for the drug, have been attributed to the vasodilatory properties of riociguat [21]. Although the overall frequency of AEs or SAEs did not differ greatly between riociguat-newly treated and riociguat-pretreated patients, numerically more events of hypotension were reported in newly treated patients, as was discontinuation because of AEs or SAEs. The higher frequency of hypotension might be partly explained by a more severe disease state (as indicated by 6MWD and WHO FC) and partly by more frequent monitoring during dose-adjustment periods. 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. Patients enrolled in disease registries as prevalent cases may be more likely to have stable disease than incident patients [23]. In our post hoc analysis,

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

	Riociguat-pretreated[a] (n = 537)	Riociguat-newly treated[b] (n = 419)
Age, years	65.9 ± 14.1	66.8 ± 13.3
Age group, years, n (%)		
< 65	218 (40.6)	148 (35.3)
65 to < 75	138 (25.7)	122 (29.1)
≥ 75	181 (33.7)	149 (35.6)
Female sex, n (%)	337 (62.8)	233 (55.6)
BMI, kg/m^2	29.1 ± 19.5	28.0 ± 6.3
BMI category, kg/m^2, n (%)		
< 18.5	15 (2.8)	9 (2.1)
18.5 to < 25	164 (30.5)	126 (30.1)
25 to < 30	191 (35.6)	157 (37.5)
≥ 30	167 (31.1)	127 (30.3)
Smoking status, n (%)		
Never	332 (61.8)	270 (64.4)
Former	181 (33.7)	133 (31.7)
Current	24 (4.5)	16 (3.8)
Prevalent (disease duration ≥ 6 months), n (%)	481 (89.6)	232 (55.4)
Incident (disease duration < 6 months)	28 (5.2)	169 (40.3)
Duration status unknown, n (%)	28 (5.2)	18 (4.3)
Age at initial PH diagnosis, years	61.6 ± 14.8 (n = 509)	64.2 ± 13.9 (n = 403)
Median (IQR) PH disease duration, years	2.9 (1.5–5.6)	0.8 (0.2–4.0)
Persistent CTEPH following PEA, n (%)	133 (24.8)	74 (17.7)
Persistent CTEPH following BPA, n (%)	16 (3.0)	10 (2.4)
WHO FC, % (I/II/III/IV/unknown)	5.6/45.1/43.6/2.8/3.0	1.9/29.4/58.5/3.3/6.9
BNP, pg/mL (median, range)	107 (5–3560) (n = 79)	171 (6–5844) (n = 69)
NT-proBNP, pg/mL (median, range)	483 (16–177 759) (n = 320)	813 (17–48 858) (n = 220)
6MWD, m	382 ± 122 (n = 477)	341 ± 133 (n = 334)
6MWD, n (%)		
< 320 m[c]	152 (28.3)	138 (32.9)
≥ 320 m	325 (60.5)	196 (46.8)
< 380 m	219 (40.8)	202 (48.2)
≥ 380 m[c]	258 (48.0)	132 (31.5)
Missing	60 (11.2)	85 (20.3)
EQ-5D VAS	63.6 ± 19.7 (n = 144)	60.1 ± 22.1 (n = 85)
Borg Dyspnea Index	3.7 ± 2.2 (n = 403)	4.0 ± 2.3 (n = 298)
mPAP, mmHg	43.3 ± 11.8 (n = 462)	42.8 ± 11.2 (n = 388)
PVR, dyn•s•cm^{-5}	675 ± 575 (n = 413)	626 ± 400 (n = 354)
PAWP, mmHg	11.2 ± 5.0 (n = 436)	10.9 ± 4.9 (n = 373)
Cardiac index, L/min/m^2	2.8 ± 5.0 (n = 409)	2.7 ± 3.7 (n = 347)
RAP, mmHg	9.3 ± 5.9 (n = 389)	8.6 ± 5.1 (n = 321)
SvO_2, %	63.6 ± 9.5 (n = 323)	63.9 ± 8.9 (n = 290)
Riociguat daily dose at initial study visit, mg		
Mean	7.1 ± 1.1	6.6 ± 1.6 (n = 397)
Median (range)	7.5 (1.5–7.5)	7.5 (1.5–7.5) (n = 397)

(*continued on next page*)

Table 3 (*continued*)

	Riociguat-pretreated[a] (n = 537)	Riociguat-newly treated[b] (n = 419)
Riociguat median daily dose at initial study visit, mg, n (%)		
≤2.5	6 (1.1)	7 (1.7)
> 2.5 to 4.5	34 (6.3)	74 (17.7)
> 4.5 to 6	51 (9.5)	39 (9.3)
> 6 to 7.5	446 (83.1)	277 (66.1)
Missing	0	22 (5.3)
PAH-approved regimen at initial study visit, n (%)		
Riociguat monotherapy[d]	403 (75.1)	355 (84.7)
Riociguat combination therapy[e,f]	134 (25.0)	64 (15.3)
Riociguat + ERA	112 (20.9)	58 (13.8)
Riociguat + ambrisentan	21 (3.9)	15 (3.6)
Riociguat + bosentan	47 (8.8)	20 (4.8)
Riociguat + macitentan	44 (8.2)	23 (5.5)
Riociguat + prostanoid	6 (1.1)	3 (0.7)
Riociguat + iloprost	3 (0.6)	3 (0.7)
Riociguat + intravenous treprostinil	2 (0.4)	0 (0.0)
Riociguat + intravenous epoprostenol	1 (0.2)	0 (0.0)
Riociguat + ERA + prostanoid	16 (3.0)	3 (0.7)
Concomitant CCB, n (%)	13 (2.4)	9 (2.1)
Concomitant anticoagulation, n (%)		
Oral anticoagulation	482 (89.8)	379 (90.5)
Vitamin K antagonist	311 (57.9)	195 (46.5)
Direct oral anticoagulant	84 (15.6)	106 (25.3)
Other oral anticoagulation[g]	87 (16.2)	72 (17.2)
Other anticoagulant[g]	34 (6.3)	32 (7.6)
Concomitant antiplatelet agents, n (%)	16 (3.0)	28 (6.7)
Comorbidity, n (%)		
At least one medical history finding	509 (94.8)	392 (93.6)
Arterial hypertension	231 (43.0)	214 (51.1)
Venous thromboembolism	223 (41.5)	208 (49.6)
Thyroid disease	100 (18.6)	83 (19.8)
Cancer	67 (12.5)	56 (13.4)
Coronary heart disease	67 (12.5)	55 (13.1)
Diabetes mellitus	66 (12.3)	57 (13.6)
Obstructive sleep apnea	65 (12.1)	34 (8.1)
History of hemoptysis/lung bleeding	23 (4.3)	14 (3.3)
Other	428 (79.7)	331 (79.0)

6MWD, 6-min walking distance; BMI, body mass index; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CCB, calcium channel blocker; CTEPH, chronic thromboembolic pulmonary hypertension; EQ-5D VAS, EuroQoL 5-dimensional Visual Analog Score; ERA, endothelin receptor antagonist; 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; PEA, pulmonary endarterectomy; 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.
[a] Receiving riociguat for ≥ 3 months before entry (n = 537 unless otherwise indicated).
[b] Receiving riociguat for < 3 months before entry (n = 419 unless otherwise indicated).
[c] Thresholds chosen (380 m prespecified) based on available (6MWD) cohort data at the time indicating good or poor prognosis in PAH.
[d] Patients receiving riociguat but no ERA or prostanoid.
[e] Patients receiving riociguat + ERA or prostanoid or both.
[f] No patient received concomitant PDE5i during the study.
[g] As indicated by the investigator on the CRF.

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 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 CTEPH disease duration in the prevalent group.

4.2. Comparison with other studies

Compared with the 247 non-operable patients described in the international prospective CTEPH registry [9,24], CTEPH patients in EXPERT had less severe functional impairment, with 53.1% categorized as WHO FC III/IV at baseline versus 83.0% and a slightly higher mean 6MWD at baseline (365 vs. 315 m). The international registry enrolled only incident patients, whereas 74.6% of patients with CTEPH in EXPERT had prevalent disease. In a prospective study of 392 patients newly diagnosed with CTEPH in Germany, riociguat was the initial treatment in 81.1% of patients who received medical therapy, illustrating the importance of obtaining safety data for riociguat [25]. The patients in this study had generally similar characteristics to those in the EXPERT population.

The estimated survival rate in patients with CTEPH in EXPERT (94.7%, 85.7%, and 79.3% at 1, 2, and 3 years, respectively) appears to be higher than in non-operable patients in the international CTEPH registry (88%, 79%, and 70% at 1, 2, and 3 years, respectively) [24], non-PEA patients in the Giessen registry (84.5% at 1 year and 72.5% at 3 years) [26], US veterans evaluated in a retrospective analysis (89.2%, 81.4%, and 72.7% at 1, 3, and 5 years, respectively) [27], and patients in several other registries [13,14,28–30]. In an analysis from COMPERA, 561 medically treated patients with CTEPH were graded as at low, intermediate, or high risk for death based on their WHO FC, 6MWD, BNP/NT-proBNP,

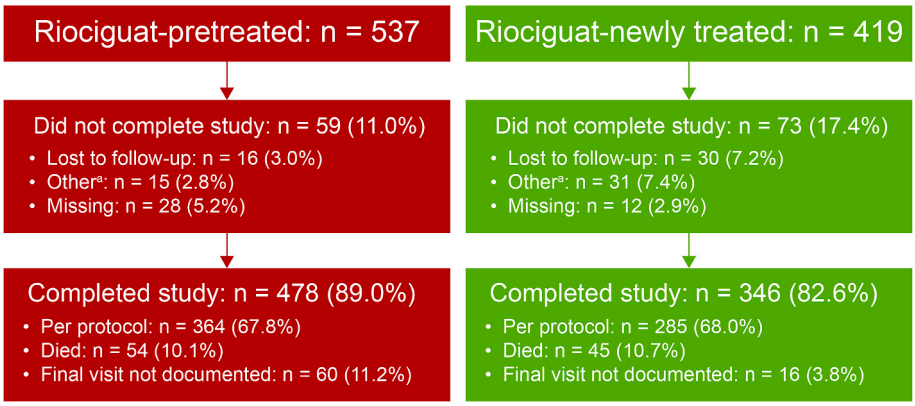

Fig. 3. Disposition of riociguat-pretreated and riociguat-newly treated patients with CTEPH. Chart shows primary reason for discontinuation.
[a]Other reasons for not completing the study are listed in Supplementary Table 1.

RAP, CI, and SvO_2 [31]. The estimated 1-year survival rate was 98.6%, 94.9%, and 75.5% in the low-, intermediate-, and high-risk groups, respectively. The baseline characteristics of CTEPH patients in EXPERT and their estimated survival were closest to those of the intermediate-risk COMPERA group.

Registries provide important information about the safety of drugs in clinical practice and thus supplement the information gained from selected populations under the closely controlled conditions of clinical trials. They may also detect previously unsuspected safety signals. No such signals were identified in EXPERT. Limitations inherent in registries including confounding, lack of randomization, missing values, and the hazards of generalizing data from the registry population to other populations [32], 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. Strengths of EXPERT include the relatively long observation time (median: 504 days), the large number (956) of patients with CTEPH, the large proportion of patients completing the study. The planned enrollment for the entire study was 900 patients to allow for detection of ≥ 3 "uncommon" AEs with an incidence ≥ 0.5%. Given that 956 patients with CTEPH were enrolled, there were enough patients in the CTEPH cohort alone to achieve this power level. The availability of safety data in

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

	Riociguat-pretreated[a] (n = 537)	Riociguat-newly treated[b] (n = 419)
AEs, n (%)		
Any AE	345 (64.2)	270 (64.4)
Most common AEs[c], n (%)		
Peripheral edema/edema	73 (13.6)[d]	39 (9.3)[e]
Dyspnea	50 (9.3)	31 (7.4)
Dizziness	42 (7.8)	30 (7.2)
RV failure/cardiac failure	40 (7.4)[f]	34 (8.1)[g]
Pneumonia	31 (5.8)	17 (4.1)
Cough	27 (5.0)	16 (3.8)
Hypotension	13 (2.4)	24 (5.7)
Dyspepsia	12 (2.2)	21 (5.0)
Any drug-related AE[h]	53 (9.9)	95 (22.7)
Discontinuation due to AE	21 (3.9)	34 (8.1)
SAEs, n (%)		
Any SAE	199 (37.1)	166 (39.6)
Most common SAEs[i], n (%)		
RV failure/cardiac failure	39 (7.3)[j]	32 (7.6)[k]
Pneumonia	26 (4.8)	13 (3.1)
Dyspnea	17 (3.2)	17 (4.1)
Syncope	14 (2.6)	10 (2.4)
PH[l]	15 (2.8)	7 (1.7)
Pulmonary embolism	3 (0.6)	9 (2.1)
Any drug-related SAE[h]	13 (2.4)	21 (5.0)
Discontinuation due to SAE	17 (3.2)	21 (5.0)

AE, adverse event; PH, pulmonary hypertension; RV, right ventricular; SAE, serious adverse event.
[a] Receiving riociguat for ≥ 3 months before entry. Median (range) duration of observation and riociguat treatment (days): 532.0 (0.0–1346.0); 506.0 (0.0–1346.0).
[b] Receiving riociguat for < 3 months before entry. Median (range) duration of observation and riociguat treatment (days): 475.0 (0.0–1367.0); 455.0 (0.0–1367.0).
[c] Preferred-term AEs reported in ≥ 5% of patients in either group.
[d] Peripheral edema in 46 patients (8.6%) and edema in 30 patients (5.6%).
[e] Peripheral edema in 27 patients (6.4%) and edema in 12 patients (2.9%).
[f] RV failure in 34 patients (6.3%) and cardiac failure in 7 patients (1.3%).
[g] RV failure in 27 patients (6.4%) and cardiac failure in 9 patients (2.1%).
[h] Investigator's causality assessment.
[i] Preferred-term SAEs reported in ≥ 2% of patients in either group.
[j] RV failure in 34 patients (6.3%) and cardiac failure in 6 patients (1.1%).
[k] RV failure in 25 patients (6.0%) and cardiac failure in 9 patients (2.1%).
[l] Preferred term for worsening of the condition.Note. Patients with peripheral edema/edema or RV failure/cardiac failure could have both events.

Table 5
AEs and SAEs of special interest.

	All CTEPH (n = 956)[a]	Riociguat-pretreated[b] (n = 537)	Riociguat-newly treated[c] (n = 419)
Absolute AE rates, n (%)			
Hypotension	37 (3.9)	13 (2.4)	24 (5.7)
Hemoptysis/pulmonary hemorrhage	26 (2.7)	15 (2.8)	11 (2.6)
Exposure-adjusted AE rates (95% CI)[d]			
Hypotension	2.7 (2.0–3.7)	1.7 (0.9–2.7)	4.3 (2.8–6.2)
Hemoptysis/pulmonary hemorrhage	2.2 (1.5–3.0)	1.9 (1.1–3.0)	2.6 (1.5–4.1)
Absolute SAE rates, n (%)			
Hypotension	4 (0.4)	3 (0.6)	1 (0.2)
Hemoptysis/pulmonary hemorrhage	16 (1.7)	8 (1.5)	8 (1.9)
Exposure-adjusted SAE rates (95% CI)[d]			
Hypotension	0.3 (0.1–0.7)	0.4 (0.1–0.9)	0.2 (0.0–0.8)
Hemoptysis/pulmonary hemorrhage	1.4 (0.9–2.1)	1.1 (0.5–1.9)	1.9 (1.0–3.2)

AE, adverse event; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; SAE, serious adverse event.
[a] Median (range) duration of observation and riociguat treatment (days): 504.0 (0.0–1367.0); 493.5 (0.0–1367.0).
[b] Receiving riociguat for ≥ 3 months before entry. Median (range) duration of observation and riociguat treatment (days): 532.0 (0.0–1346.0); 506.0 (0.0–1346.0).
[c] Receiving riociguat for < 3 months before entry. Median (range) duration of observation and riociguat treatment (days): 475.0 (0.0–1367.0); 455.0 (0.0–1367.0).
[d] Rate per 100 patient-years, calculated by the number of events observed divided by (total drug exposure in years/100).

patients receiving riociguat either as monotherapy or as part of a combination regimen at baseline was also a strength of the study.

5. Conclusion

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

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, ELPEN Pharmaceuticals, GSK, Pfizer, Lilly, and United Therapeutics, and research support from GSK, ELPEN Pharmaceuticals, and Galenica. Dr Henning Gall has received honoraria and/or other support from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. Dr Pavel Jansa reports consultancy and speaker fees from MSD, AOP Orphan, and Actelion. Prof Ekkehard Grünig reports research grants and speaker honoraria/consultancy fees from Actelion and Bayer/MSD, research grants from GSK, United Therapeutics, Bellerophon, OMT GmbH, Pfizer, Reata, and Novartis, and speaker honoraria from Bial, Medscape, and OrPha Swiss GmbH. Prof David Pittrow reports personal fees from Actelion, Bayer AG, Aspen, Boehringer Ingelheim, Sanofi, Biogen, Shire, and MSD outside the submitted work. Silvia Ulrich reports research grants and personal fees from Actelion, Bayer, MSD, and Orpha Swiss. Tobias J. Lange has received personal fees from Actelion, MSD, Pfizer, and OMT orphan. Dr Iraklis Tsangaris reports speaker and consultancy fees from Actelion, Bayer AG, ELPEN, GSK, MSD, Pfizer, and United Therapeutics. Stephan Rosenkranz reports remunerations for lectures and/or consultancy from Abbott, Actelion, Arena, Bayer, Ferrer, GSK, MSD, Novartis, Pfizer, and United Therapeutics; and research support to his institution from Actelion, Bayer, Novartis, Pfizer, and United Therapeutics. Repke J. Snijder reports grants from Pfizer and Actelion Pharmaceuticals. Prof Iveta Šimková reports consultancy and speaker fees from MSD, AOP Orphan, and Actelion. Dr Marc Humbert reports grants and personal fees from Bayer and GSK, and personal fees from Actelion, Merck, and United

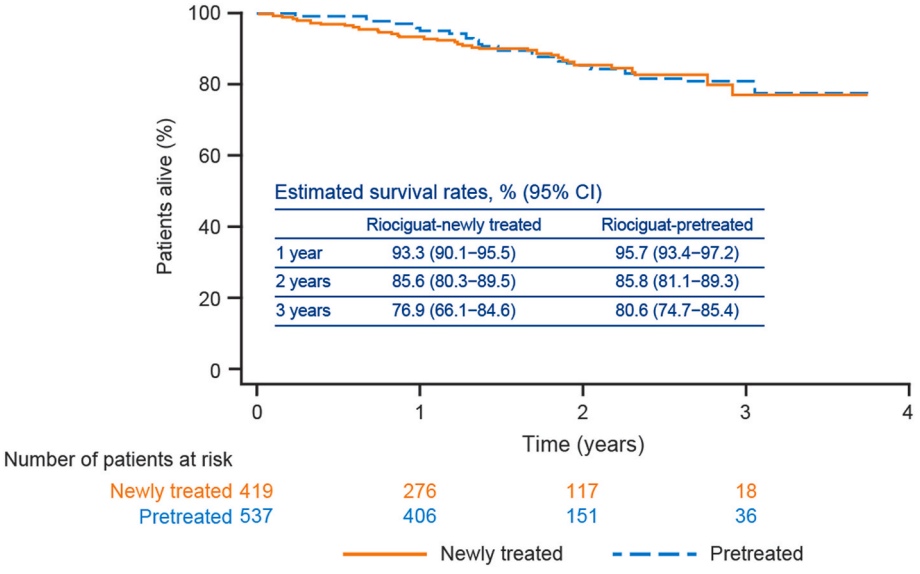

Fig. 4. Kaplan–Meier survival curves for riociguat-newly treated and riociguat-pretreated patients. CI, confidence interval.

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Appendix A. Supplementary data

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Credit author statement

Marius M. Hoeper. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Miguel-Angel Gomez Sanchez. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Marc Humbert. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

David Pittrow. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; project administration; approval of final draft for submission.

Gérald Simonneau. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Hossein-Ardeschir Ghofrani. Conceptualization; methodology; investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Henning Gall. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Ekkehard Grünig. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Hans Klose. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Michael Halank. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

David Langleben. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Repke J. Snijder. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Pilar Escribano Subias. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Lisa M. Mielniczuk. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Tobias J. Lange. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Jean-Luc Vachiéry. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Hubert Wirtz. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Douglas S. Helmersen. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Iraklis Tsangaris. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Joan A. Barberà. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Joanna Pepke-Zaba. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Anco Boonstra. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Stephan Rosenkranz. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Silvia Ulrich. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Regina Steringer-Mascherbauer. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Marion Delcroix. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Pavel Jansa. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Iveta Šimková. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

George Giannakoulas. Investigation; resources; writing – review & editing; supervision; approval of final draft for submission.

Jens Klotsche. Conceptualization; methodology; software; validation; formal analysis; resources; data curation; writing – review & editing; visualization; approval of final draft for submission.

Evgenia Williams. Validation; formal analysis; data curation; writing – review & editing; approval of final draft for submission.

Christian Meier. Conceptualization; methodology; validation; writing – review & editing; supervision; project administration; funding acquisition; approval of final draft for submission.

Collaborators. Investigation; resources; supervision.

References

[1] N. Galiè, et al., ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC) International Society for Heart and Lung Transplantation (ISHLT), Eur. Respir. J. 46 (4) (2015) 903–975.

[2] G. Simonneau, et al., Updated clinical classification of pulmonary hypertension, J. Am. Coll. Cardiol. 62 (Suppl 25) (2013) D34–D41.

[3] N.H. Kim, et al., Chronic thromboembolic pulmonary hypertension, J. Am. Coll. Cardiol. 62 (25 Suppl) (2013) D92–D99.

[4] P. Fedullo, et al., Chronic thromboembolic pulmonary hypertension, Am. J. Respir. Crit. Care Med. 183 (12) (2011) 1605–1613.

[5] M. Delcroix, et al., ERS statement on chronic thromboembolic pulmonary hypertension, Eur. Respir. J. (2020) in press.

[6] E. Mayer, et al., Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry, J. Thorac. Cardiovasc. Surg. 141 (3) (2011) 702–710.

[7] D. Jenkins, Pulmonary endarterectomy: the potentially curative treatment for patients with chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 24 (136) (2015) 263–271.

[8] D. Jenkins, et al., Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (143) (2017).

[9] J. Pepke-Zaba, et al., Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry, Circulation 124 (18) (2011) 1973–1981.

[10] D. Jenkins, et al., State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management, Eur. Respir. Rev. 21 (123) (2012) 32–39.

[11] D.H. Freed, et al., Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension, J. Thorac. Cardiovasc. Surg. 141 (2) (2011) 383–387.

[12] E. Mayer, Surgical and post-operative treatment of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 19 (115) (2010) 64–67.

[13] J. Hurdman, et al., ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre, Eur. Respir. J. 39 (4) (2012) 945–955.

[14] J.E. Cannon, et al., Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the UK national cohort, Circulation 133 (18) (2016) 1761–1771.

[15] H.A. Ghofrani, et al., Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, N. Engl. J. Med. 369 (4) (2013) 319–329.

[16] G. Simonneau, et al., Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial, Lancet Respir. Med. 4 (5) (2016) 372–380.

[17] N.H. Kim, et al., Chronic thromboembolic pulmonary hypertension, Eur. Respir. J. 53 (1) (2019).

[18] M. Hoeper, et al., Riociguat treatment in patients with pulmonary arterial hypertension: Final safety data from the EXPERT registry, Respir. J. 53 (1) (2020) in press.

[19] G. Simonneau, et al., Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2), Eur. Respir. J. 45 (5) (2015) 1293–1302.

[20] V. McLaughlin, et al., Riociguat in patients with chronic thromboembolic pulmonary hypertension: results from an early access study, BMC Pulm. Med. 17 (1) (2017) 216–224.

[21] Bayer-AG, Adempas. Summary of Product Characteristics, European Medicines Agency website. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Product_Information/human/002737/WC500165034.pdf [cited 2019 May 22nd].

[22] Bayer Pharma AG, US prescribing information: ADEMPAS (riociguat) tablets, for oral use, 2018. https://labeling.bayerhealthcare.com/html/products/pi/Adempas_PI.pdf. (Accessed 14 January 2021).

[23] M. Humbert, et al., Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension, Eur. Respir. J. 36 (3) (2010) 549–555.

[24] M. Delcroix, et al., Long-term outcome of patients with chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry, Circulation 133 (2016) 859–871.

[25] T. Kramm, et al., Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany, Clin. Res. Cardiol. 107 (7) (2018) 548–553.

[26] H. Gall, et al., The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups, J. Heart Lung Transplant. (2017) S1053–S2498.

[27] A.W. Trammell, et al., EXPRESS: mortality in U.S. veterans with pulmonary hypertension: a retrospective analysis of survival by subtype and baseline factors, Pulm. Circ. (2019), 2045894019825763.

[28] P. Escribano-Subias, et al., Management and outcomes in chronic thromboembolic pulmonary hypertension: from expert centers to a nationwide perspective, Int. J. Cardiol. 203 (2016) 938–944.

[29] S. Mueller-Mottet, et al., Long-term data from the Swiss pulmonary hypertension registry, Respiration 89 (2) (2015) 127–140.

[30] R. Condliffe, et al., Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension, Am. J. Respir. Crit. Care Med. 177 (10) (2008) 1122–1127.

[31] M. Delcroix, et al., Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients, Eur. Respir. J. 52 (5) (2018), 1800248.

[32] M.D. McGoon, et al., Pulmonary arterial hypertension: epidemiology and registries, J. Am. Coll. Cardiol. 62 (25 Suppl) (2013) D51–D59.