Respiratory Medicine 128 (2017) 50–56

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Riociguat for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: Results from a phase II long-term extension study

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ARTICLE INFO

Article history:
Received 20 January 2017
Received in revised form
30 April 2017
Accepted 15 May 2017
Available online 16 May 2017

Keywords:
Clinical study
Pulmonary hypertension
Soluble guanylate cyclase stimulator
Riociguat

ABSTRACT

Background: Riociguat was well tolerated and improved exercise and functional capacity in patients with pulmonary arterial hypertension (PAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH) in a 12-week Phase II trial. We present final data from the long-term extension phase of this study.

Methods: During this multicenter, open-label, uncontrolled long-term extension study, riociguat dose could be changed at the physician's discretion (range 0.5–2.5 mg three times daily). The primary outcome was long-term safety and tolerability of riociguat; secondary outcomes included 6-minute walking distance, World Health Organization functional class, survival, and clinical worsening-free survival.

Results: Sixty-eight patients (inoperable CTEPH, n = 41; PAH, n = 27) entered the long-term extension. Median treatment duration at the final data cut-off was 77 months. The most common adverse events were nasopharyngitis (57%) and peripheral edema (37%). Three patients (4%) experienced serious adverse events of hemoptysis: two moderate, one severe, none fatal or considered drug-related. At Month 48, 6-minute walking distance increased from baseline by 69 ± 105 m, and World Health Organization functional class improved/stabilized/worsened versus baseline in 50/45/5% of patients. Three-year survival and clinical worsening-free survival were 91% and 49%, respectively (with patients censored if they withdrew without experiencing an event). Starting a new PAH treatment was the most frequent clinical worsening event.

Abbreviations: 6MWD, 6-minute walking distance; AE, adverse event; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; LTE, long-term extension; NO, nitric oxide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SAE, serious adverse event; SD, standard deviation; sGC, soluble guanylate cyclase; tid, three times daily; WHO FC, World Health Organization functional class.

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http://dx.doi.org/10.1016/j.rmed.2017.05.008

Conclusions: Improvements in exercise and functional capacity were maintained at 4 years in patients remaining on treatment, with no new safety signals identified. These data support riociguat as a long-term treatment option for PAH and inoperable CTEPH.
Trial registered at: ClinicalTrials.gov.
Registration number: NCT00454558.

1. Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are serious and progressive diseases, characterized by an increase in pulmonary vascular resistance, which can ultimately lead to death due to right heart failure [1]. PAH is caused by remodeling of the small pulmonary arteries, whereas CTEPH is a result of obstructive thromboembolic material in the pulmonary vasculature, though CTEPH can also have a distal vascular remodeling component similar to that observed in idiopathic PAH [2,3].

PAH is primarily treated pharmacologically, and therapies include prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, and the soluble guanylate cyclase (sGC) stimulator riociguat [1,4]. For CTEPH, pulmonary endarterectomy (PEA) is the gold standard treatment as it is potentially curative [1,2,5]. However, approximately one-third of patients are considered inoperable, and others develop persistent/recurrent PH following PEA [6–12]. Such patients may benefit from pharmacologic therapy [1,13].

The sGC stimulator riociguat is approved for the treatment of both PAH and inoperable or persistent/recurrent CTEPH [1]. Riociguat has a dual mode of action, sensitizing sGC to endogenous nitric oxide (NO) and directly stimulating sGC independently of NO. This results in increased production of cyclic guanosine monophosphate, leading to vasodilation and anti-inflammatory, antiproliferative, and anti-fibrotic effects [14].

In a 12-week, open-label, uncontrolled, Phase II trial in patients with PAH or inoperable CTEPH, riociguat was well tolerated and led to clinically relevant improvements in 6-minute walking distance (6MWD), World Health Organization functional class (WHO FC), and hemodynamic parameters [15]. Here we present the final safety and efficacy data from the long-term extension (LTE) phase of this study, with a median riociguat treatment duration of >6 years, in which we hypothesized that the benefits of riociguat seen in the initial phase of the study would continue into the LTE.

2. Materials and methods

2.1. Study design and patients

This was a multicenter, open-label, uncontrolled study performed in 13 of the 15 centers across Germany that participated in the initial 12-week Phase II study. Full details of inclusion and exclusion criteria have been reported elsewhere [15]. In brief, patients with PAH or inoperable CTEPH (WHO FC II/III, mean pulmonary vascular resistance >300 dyn $s \cdot cm^{-5}$, and mean pulmonary arterial pressure ≥25 mmHg) who had successfully completed the initial 12-week study were invited to participate in the LTE. During the initial 12-week study, the riociguat dose was individually adjusted over a period of 8 weeks from a starting dose of 1 mg three times daily (tid) to a maximum of 2.5 mg tid, according to systolic blood pressure and signs and symptoms of hypotension [15]. During the LTE, the dose of riociguat could be changed at the discretion of the physician within the range of 0.5 mg tid to 2.5 mg tid.

The use of established therapy with ERAs in patients with PAH was permitted at entry into the initial 12-week study, and general supportive therapy with diuretics, anticoagulants, and calcium channel blockers was permitted in all patients. During the LTE, patients were permitted to receive add-on therapy with ERAs or prostanoids at the discretion of the study investigator. NO donors and specific or non-specific PDE5 inhibitors were not permitted.

The study was carried out in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and is registered at ClinicalTrials.gov (NCT00454558). The study protocol was approved by the ethics committees of all participating centers and all patients gave written informed consent.

2.2. Outcomes

The primary outcome was the long-term safety and tolerability of riociguat. Secondary outcomes included 6MWD, WHO FC, survival, and clinical worsening-free survival. Clinical worsening was defined as any of the following events: death, heart/lung transplantation, atrial septostomy, PEA, or start of new treatment for pulmonary hypertension (PH). No invasive hemodynamic assessment was planned as part of the study protocol.

2.3. Statistical analysis

Statistical analyses in this uncontrolled exploratory trial were descriptive and no formal statistical sample size estimation was performed. The SAS® software package (SAS Institute, Cary, NC, USA) was used for statistical evaluation.

All patients entering the LTE were included in the safety assessment. AEs in the LTE were defined as any AE starting or worsening after the first dose of LTE study medication, up until 30 days after treatment was stopped.

6MWD, WHO FC, modified Borg dyspnea, and NT-proBNP data are presented to Month 48, after which patient numbers were too low for meaningful analysis. Only patients remaining on riociguat at the respective timepoints were included in these analyses; missing data were not imputed. Survival, clinical worsening-free survival, time to addition of concomitant PH treatment, and time to discontinuation were analyzed using Kaplan–Meier plots up to Month 76. For the survival and clinical worsening-free survival analyses, patients were censored if they had withdrawn without experiencing an event.

3. Results

3.1. Study population

Sixty-eight patients entered the LTE (Fig. 1), of whom 41 had inoperable CTEPH and 27 had PAH. Baseline characteristics at entry into the LTE are shown in Table 1. As observed at the start of the initial 12-week study [15], baseline 6MWD was somewhat lower in

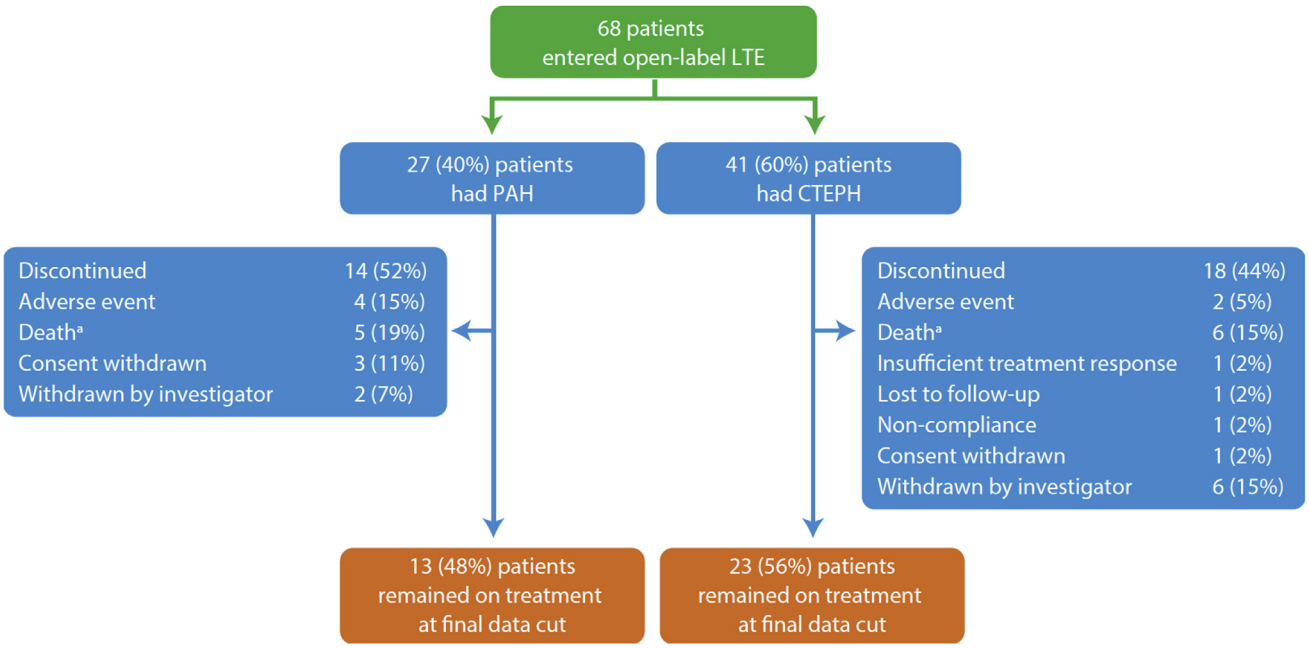

Fig. 1. Patient disposition.
CTEPH = chronic thromboembolic pulmonary hypertension; LTE = long-term extension; PAH = pulmonary arterial hypertension.
[a]Two additional patients (one with PAH and one with CTEPH) died after discontinuing riociguat.

Table 1
Baseline characteristics in patients entering the LTE.

Characteristic	PAH (n = 27)	CTEPH (n = 41)	Total (n = 68)
Age, years	56.1 (19–73)	61.6 (37–76)	59.4 (19–76)
Ethnic origin white	27 (100)	41 (100)	68 (100)
Female	20 (74)	18 (44)	38 (56)
Body mass index, kg/m^2	26.9 (18.6–38.1)	25.6 (17.0–33.3)	26.1 (17.0–38.1)
6MWD, m	406.7 (150–630)	447.6 (260–727)[a]	430.9 (150–727)[b]
WHO FC			
I	1 (4)	1 (2)	2 (3)
II	9 (33)	21 (51)	30 (44)
III	17 (63)	19 (46)	36 (53)
IV	0	0	0

6MWD = 6-minute walking distance; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; WHO FC = World Health Organization functional class.
Data are number (%) or mean (range). The values listed for 6MWD and WHO FC correspond to values at the end of the initial 12-week study. [a] n = 39; [b] n = 66.

patients with PAH than in those with CTEPH. Baseline WHO FC was also slightly worse in patients with PAH than in those with CTEPH.

Thirty-six patients (53%) were still receiving riociguat treatment at the final data cut-off (September 2014), and 32 (47%) had discontinued treatment (Fig. 1). The time to discontinuation of riociguat from all causes is shown in Fig. 2. At the final data cut-off, the median treatment duration was 77 months (range 3–87 months). At the end of the LTE or at withdrawal, 50 (74%) patients were receiving the maximum 2.5 mg tid dose of riociguat.

At entry to the LTE, six (9%) patients were receiving concomitant therapy with bosentan; the remaining patients were treatment naïve. During the course of the LTE, a further 30 (44%) patients initiated concomitant therapy with ERAs and/or prostanoids. The remaining 32 (47%) patients remained on riociguat monotherapy until the final data cut-off or discontinuation. Of the 36 patients who were still receiving riociguat at the final data cut-off, 16 (44%) were receiving concomitant therapy with ERAs and/or prostanoids.

3.2. Safety

A summary of riociguat safety data from the LTE is shown in Table 2. AEs were reported by 93% of patients and were evenly distributed across patients with PAH and CTEPH. The most common AEs were nasopharyngitis (57%; 0% considered drug-related) and peripheral edema (37%; 3% considered drug-related).

Serious adverse events (SAEs) were reported by 76% of patients and were more common amongst patients with CTEPH compared with PAH (83% vs 67%, respectively). The most common SAEs were right ventricular failure, syncope, and worsening PH (each occurring in 19% of patients). Three (4%) cases of syncope and two (3%) cases of worsening PH were considered drug-related. Three patients (4%) experienced SAEs of hemoptysis (all patients with PAH); two of the SAEs of hemoptysis were moderate in severity, and one was severe; none were considered drug-related and none were fatal. The exposure-adjusted incidence of hemoptysis SAEs in the LTE was 1.0 event per 100 patient-years.

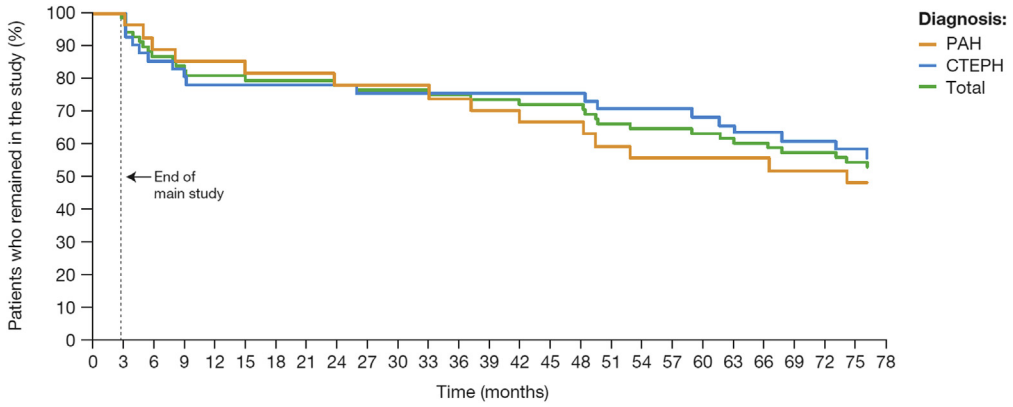

Fig. 2. Kaplan–Meier plot of time to discontinuation of riociguat for the 68 patients who entered the LTE.
CTEPH = chronic thromboembolic pulmonary hypertension; LTE = long-term extension; PAH = pulmonary arterial hypertension.

Six (9%) patients discontinued riociguat due to AEs as the primary reason. These were clinical worsening of PH (n = 2), clinical worsening of PAH (n = 1), pneumonia (n = 1), hepatocellular carcinoma (n = 1), and headache, symptomatic flush, and vertigo related to a vascular event (n = 1).

3.3. Secondary outcomes: long-term change from baseline in efficacy

3.3.1. 6MWD

The change from baseline in 6MWD during the LTE, in patients who remained on riociguat therapy at each timepoint, is shown in Fig. 3. Mean ± standard deviation (SD) 6MWD increased from baseline by 69 ± 105 m (n = 42) in the overall population at Month 48, and by 87 ± 138 m (n = 15) and 59 ± 82 m (n = 27) in patients with PAH and CTEPH, respectively.

3.3.2. WHO FC

Change from baseline in WHO FC up to Month 48 of the LTE, in patients who remained on riociguat therapy at each timepoint, is shown in Fig. 4. At Month 48, WHO FC had improved/stabilized/worsened versus baseline in 50/45/5% of the overall population (n = 44), 56/44/0% of patients with PAH (n = 16), and 46/46/7% of patients with CTEPH (n = 28).

3.3.3. Survival and clinical worsening

The frequency of clinical worsening events during the LTE are shown in Table 3. In total, 43 out of 68 (63%) patients experienced clinical worsening events. Start of new PH treatment was the most frequent event, occurring in 35 (51%) patients. Rates of patients in the overall population who had not begun a new PH treatment at 9, 36, and 72 months were 78%, 53%, and 42%, respectively.

A total of 13 out of 68 (19%) patients died during the LTE, including two patients who died after discontinuing riociguat. All causes of death were assessed as being unrelated to study drug and eight (12%) were due to progression of PAH or CTEPH, including five cases of right heart failure. Fig. 5 shows Kaplan–Meier plots of survival and clinical worsening-free survival during the LTE. Clinical worsening-free survival rates in the overall population at 9, 36, and 72 months were 73%, 49%, and 35%, respectively. Survival rates in the overall population at 9, 36, and 72 months were 97%, 91%, and 81%, respectively. For the Kaplan–Meier analyses, patients were censored if they had withdrawn without experiencing an event.

Table 2
Summary of safety.

Event, n (%)[a]	PAH (n = 27)	CTEPH (n = 41)	Total (n = 68)
Any AE	26 (96)	37 (90)	63 (93)
AEs occurring in ≥15% of the total population			
Nasopharyngitis	15 (56)	24 (59)	39 (57)
Peripheral edema	9 (33)	16 (39)	25 (37)
Dizziness	13 (48)	10 (24)	23 (34)
Worsening PH	7 (26)	15 (37)	22 (32)
Edema	5 (19)	13 (32)	18 (26)
Cough	6 (22)	11 (27)	17 (25)
Hypotension	6 (22)	10 (24)	16 (24)
Respiratory tract infection	3 (11)	11 (27)	14 (21)
Syncope	6 (22)	7 (17)	13 (19)
Right ventricular failure	7 (26)	6 (15)	13 (19)
Diarrhea	5 (19)	7 (17)	12 (18)
Anemia	4 (15)	8 (20)	12 (18)
Worsening PAH	8 (30)	4 (10)	12 (18)
Bronchitis	4 (15)	7 (17)	11 (16)
Hypokalemia	1 (4)	10 (24)	11 (16)
Nausea	5 (19)	6 (15)	11 (16)
Gastroesophageal reflux disease	3 (11)	7 (17)	10 (15)
Vomiting	5 (19)	5 (12)	10 (15)
Any SAE	18 (67)	34 (83)	52 (76)
SAEs occurring in ≥10% of the total population			
Right ventricular failure	7 (26)	6 (15)	13 (19)
Syncope	6 (22)	7 (17)	13 (19)
Worsening PH	1 (4)	12 (29)	13 (19)
Worsening PAH	6 (22)	3 (7)	9 (13)
Cardiac failure	6 (22)	2 (5)	8 (12)
Discontinuation due to AE	4 (15)	2 (5)	6 (9)
Deaths[b]	5 (19)	6 (15)	11 (16)

AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; LTE = long-term extension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; SAE = serious adverse event.
[a] Median treatment duration was 77 months (range 3–87 months).
[b] Two additional patients died after discontinuing riociguat.

4. Discussion

In an initial 12-week Phase II study, treatment with riociguat was well tolerated and led to significant improvements in 6MWD and WHO FC from baseline in patients with PAH and inoperable CTEPH [15]. Here we show that riociguat was well tolerated by most patients in the LTE phase of this study, over a median treatment duration of >6 years. In addition, improvements in 6MWD and WHO FC were apparently maintained for up to 4 years. No new safety signals were identified in this LTE study and the majority of AEs were consistent with the underlying disease and the mode of

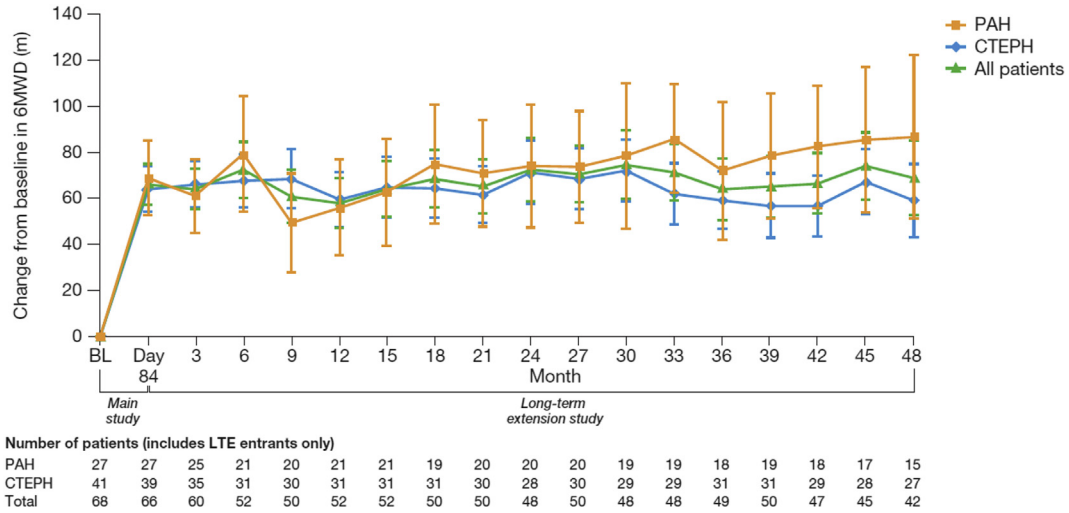

Fig. 3. Change from baseline in 6MWD.
6MWD = 6-minute walking distance; BL = baseline; CTEPH = chronic thromboembolic pulmonary hypertension; LTE = long-term extension; PAH = pulmonary arterial hypertension; SEM = standard error of the mean.
Data shown are observed values (mean ± SEM); missing data were not imputed.

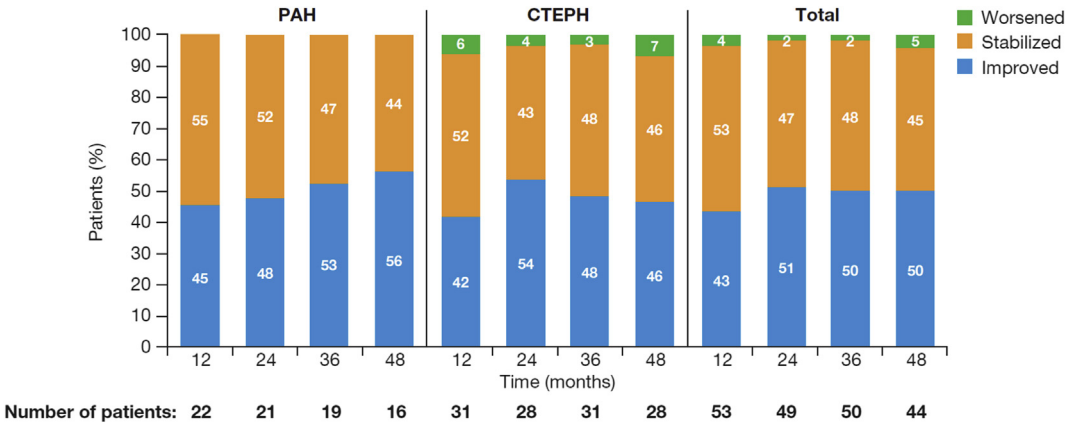

Fig. 4. Change from baseline in WHO FC.
CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; WHO FC = World Health Organization functional class.
Data shown are observed values; missing data were not imputed. Baseline was defined as the start of the initial 12-week study.
Percentages may not add up to 100% due to rounding of data.

action of riociguat. The safety profile of riociguat was similar to that observed during the initial 12-week trial and other riociguat clinical trials [15–19].

Three patients (4%) reported SAEs of hemoptysis in this study (two of which were moderate in severity and one of which was severe). This is in keeping with the Phase III LTE studies of riociguat, in which SAEs of hemoptysis or pulmonary hemorrhage were reported in 3% (PATENT-2) and 2% (CHEST-2) of patients during median treatment durations of 32 months and 27 months, respectively [18,19]. The exposure-adjusted incidence of hemoptysis SAEs in the current study (1.0 event per 100 patient-years) was also broadly consistent with results from the Phase III LTE studies (1.7 and 0.7 events per 100 patient-years in PATENT-2 and CHEST-2, respectively). The potentially increased risk of respiratory tract bleeding AEs with riociguat is reflected as a warning in the riociguat label [20,21]. Hemoptysis and pulmonary hemorrhage are known complications of pulmonary hypertension [22,23], and the incidence of hemoptysis in the current study was comparable to previous reports. For example, in a previous study of 210 patients with non-Eisenmenger PAH, moderate-to-severe hemoptysis was observed in 12 (6%) patients seen over a period of 10 years [23], while in another study of 79 patients with CTEPH, five (6%) patients suffered from moderate-to-severe hemoptysis requiring medical intervention [24].

There was a relatively high rate of clinical worsening observed in this study; the rates of clinical worsening-free survival at 9, 36, and 72 months were 73%, 49%, and 35%, respectively. As a comparison, the 2-year rates of clinical worsening-free survival in the PATENT-2 and CHEST-2 studies were 79% and 82%, respectively [18,19]. However, the high rate of clinical worsening in this study was driven primarily by patients starting new PH treatment, which may reflect the fact that riociguat was at a relatively early stage of development at the time this study was conducted, and that the study was performed in Germany where PH-specific therapies are readily available. In keeping with this, the clinical worsening event "start of new PH treatment" occurred more frequently in this study (51% of patients as a first event [11.3 cases per 100 patient-years]) than in the PATENT-2 and CHEST-2 studies (18% [11.1 cases per

Table 3
Frequency of clinical worsening events. For patients with more than one event, only the first event is shown.

Event, n (%)	PAH (n = 27)	CTEPH (n = 41)	All patients (n = 68)
Patients with clinical worsening event	17 (63)	26 (63)	43 (63)
PEA	0	6 (15)	6 (9)
Start of new PH treatment	16 (59)	19 (46)	35 (51)
Deaths[a]	1 (4)	1 (2)	2 (3)

CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectomy; PH = pulmonary hypertension. Median treatment duration was 77 months (3–87 months).
[a] This figure differs from the 13 deaths reported in the text because only the first event experienced by a patient is shown.

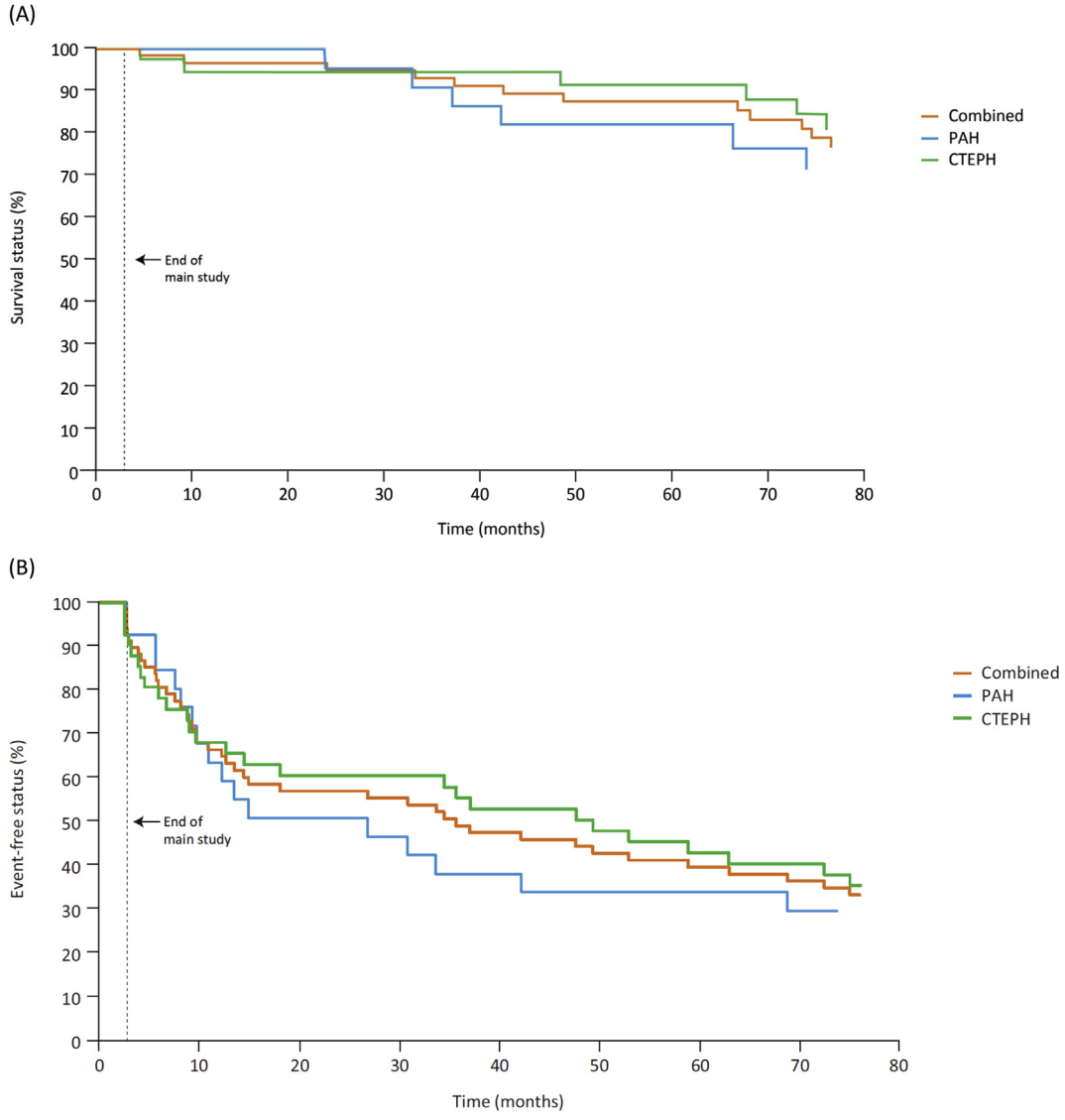

Fig. 5. Kaplan–Meier plots of (A) survival and (B) clinical worsening-free survival. Patients were censored if they had withdrawn without experiencing an event. CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.

100 patient-years] and 10% [5.0 cases per 100 patient-years], respectively, of patients overall [18,19]). Despite the high rate of clinical worsening, survival rates in this study compared favorably with those observed in the PATENT-2 and CHEST-2 studies. Survival rates in the overall study population at 9, 36, and 72 months, with patients censored if they had withdrawn, were 97%, 91%, and 81%, respectively, compared with 93% at 2 years in both PATENT-2 and CHEST-2 [18,19].

There was also a relatively high drop-out rate during the study, with 47% of patients discontinuing treatment by the final cut-off. This is likely to reflect the long duration of treatment (median 77 months) and the fact that riociguat was an experimental drug at the time the study was conducted (increasing the likelihood of withdrawn consent by the patient or physician). As a comparison, the withdrawal rates in the PATENT-2 and CHEST-2 Phase III LTE studies were 31% and 27%, respectively, but with significantly shorter treatment durations (median durations of 32 months in PATENT-2 and 27 months in CHEST-2) [18,19].

The current study has certain limitations which are common to most LTE studies. These include the lack of a placebo group, a drop-out rate of 47% during the LTE, and the fact that approximately 50% of patients were receiving concomitant therapy during the course of the LTE, making it difficult to unequivocally attribute the safety and efficacy findings solely to riociguat. In addition, patient drop-out may have resulted in bias towards those who responded well to riociguat treatment.

5. Conclusions

Riociguat was generally well tolerated over a median treatment duration of >6 years in patients with PAH and inoperable CTEPH in this Phase II LTE study. No new safety signals were identified, and improvements in 6MWD and WHO FC were maintained at 4 years in patients who remained on treatment. These data support riociguat as a favorable long-term treatment option for patients with PAH and inoperable CTEPH.

Conflicts of interest

MH reports board membership for Actelion, Bayer Pharma AG, GlaxoSmithKline, and Novartis, lecture fees from Actelion, AstraZeneca, Bayer Pharma AG, GlaxoSmithKline, Lilly, MSD, Novartis, and Pfizer, and personal fees from Actelion, Bayer Pharma AG, GlaxoSmithKline, Lilly, and Novartis. MMH has received grants, personal fees, and non-financial support from Bayer Pharma AG and personal fees from Actelion, Gilead, GlaxoSmithKline, Novartis, Merck, and Pfizer. HAG reports grants from Actelion, Bayer Pharma AG, Ergonex, and Pfizer, and personal fees from Actelion, Bayer Pharma AG, Ergonex, Gilead, GlaxoSmithKline, Merck, Novartis, and Pfizer. FJM has received lecture fees from Bayer Pharma AG. GS reports no conflicts of interest. JB reports consulting and lecture fees from Actelion, InterMune, Bayer Pharma AG, GlaxoSmithKline, Boehringer Ingelheim, consulting fees from Optima and Gilead, consulting fees and research grants from Pari-Pharma, lecture fees from Pfizer, Nycomed, AstraZeneca, and Novartis, and lecture fees and travel support from MSD. RE reports consulting fees, research grants, and lecture fees from Actelion, consulting fees and travel support from Bayer Pharma AG, and consulting fees from Novartis, GlaxoSmithKline, Lilly, and United Therapeutics. MF, PC, and SN are full-time employees of Bayer Pharma AG. FG reports grants, personal fees, and non-financial support from Bayer Pharma AG, and personal fees from Actelion, Eli Lilly, Novartis, and Pfizer.

Acknowledgments and funding

The study was supported by Bayer Pharma AG (Berlin, Germany). The sponsor was involved in designing the study, analyzing the data, and drafting the publication. Editorial assistance was provided by Adelphi Communications Ltd (Bollington, UK), supported by Bayer Pharma AG.

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