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Efficacy and safety of riociguat in combination therapy for patients with pulmonary arterial hypertension (PATENT studies)

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Abstract

Many patients with pulmonary arterial hypertension do not achieve treatment goals with monotherapy, and therefore combination therapy is becoming the standard of care. The soluble guanylate cyclase stimulator riociguat is licensed for the treatment of pulmonary arterial hypertension; here we present findings from patients who were receiving combined riociguat plus endothelin receptor antagonists or non-intravenous prostanoids in the randomized, placebo-controlled PATENT-1 study and its open-label extension (PATENT-2). Moreover, we include new data from patients receiving early sequential combination therapy (three to six months of endothelin receptor antagonist treatment) or long-term background endothelin receptor antagonist therapy (>6 months). Patients were randomized to riociguat 2.5 mg–maximum ($N = 131$ pretreated patients) and placebo ($N = 60$ pretreated patients). Riociguat improved 6-min walking distance (PATENT-1 primary endpoint), functional capacity, and hemodynamics after 12 weeks in pretreated patients. The placebo-corrected changes in 6-min walking distance were +24 m in endothelin receptor antagonist-pretreated patients and +106 m in the small group of prostanoid-pretreated patients. In the early sequential combination and long-term background endothelin receptor antagonist groups, the placebo-corrected changes in 6-min walking distance were +65 m (95% CI: 17 to 113 m) and +13 m (95% CI: –8 to 33 m), respectively. In conclusion, these data suggest that early sequential combination of an endothelin receptor antagonist plus riociguat is a feasible treatment option. Both early sequential therapy and long-term background endothelin receptor antagonist plus riociguat were well tolerated in the PATENT studies.

Keywords

hypertension, pulmonary, hemodynamics, soluble guanylyl cyclase, prostaglandins, endothelin receptor antagonists

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Introduction

Pulmonary arterial hypertension (PAH) is a chronic, life-threatening condition characterized by increased pulmonary vascular resistance (PVR) as a result of progressive vascular

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remodeling that can lead to right heart failure and, ultimately, death.[1,2] Therapy for patients with PAH has evolved considerably in recent years, and a number of classes of PAH therapies, targeting different pathologic pathways, are now available. These include endothelin receptor antagonists (ERAs), prostanoids, the prostaglandin I2 (IP) receptor agonist selexipag, phosphodiesterase type 5 (PDE5) inhibitors, and the soluble guanylate cyclase (sGC) stimulator, riociguat.[2,3]

The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) pulmonary hypertension (PH) treatment guidelines state that the overall treatment goal in patients with PAH is achieving or maintaining a low risk of mortality in one year as judged by a multi-parameter risk assessment tool and expert physician opinion.[2] However, a substantial proportion of patients with PAH do not achieve a satisfactory response on monotherapy,[4] and three-year mortality rates in incident PAH cohorts were 33–45%.[5,6] As a result, combination therapy with ≥ 2 classes of PAH-approved drugs is becoming the standard of care.[2,7] In a meta-analysis of 18 randomized controlled trials including 4162 patients with PAH, combination therapy significantly reduced the risk of clinical worsening, significantly increased 6-min walking distance (6MWD) and functional class, and improved hemodynamic parameters compared with monotherapy, although there was no effect on mortality.[8] A second meta-analysis of 17 randomized controlled trials also found a reduction in clinical worsening events with combination therapy versus monotherapy.[9] Combination therapy may be initiated upfront or in a sequential manner. To date, sequential combinations have been more widely used in clinical trials,[4] and data on upfront or early sequential combination therapy are more limited.

Riociguat is approved for the treatment of patients with PAH and those with inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgery.[10,11] In the Phase 3, 12-week PATENT-1 study, riociguat improved exercise capacity and a range of secondary endpoints in a broad population of patients with symptomatic PAH, including those pretreated with ERAs or non-intravenous prostanoids.[12] The clinical benefits of riociguat treatment were maintained at two years in the PATENT-2 open-label extension study.[13] Based on data from the PATENT study, one of the recommendations of the ESC/ERS PH treatment guidelines is sequential combination therapy with riociguat added to bosentan (Class I recommendation, Level B evidence).[2]

Here we provide an overview of riociguat combination therapy data, focusing on exploratory analyses in patients receiving early sequential combination therapy (after three to six months of ERA treatment) and long-term ERA background treatment (>6 months of ERA treatment). In addition, we present efficacy findings from the overall subgroup of patients who were pretreated with an ERA, and those who were pretreated with a non-intravenous prostanoid at entry into PATENT-1 and report long-term subgroup data from PATENT-2.

Methods

Patients and study design

Full details of the PATENT-1 and -2 studies have been published previously.[12,13] In brief, PATENT-1 was a double-blind, placebo-controlled Phase 3 study in which 443 patients (50% treatment-naïve and 50% pretreated with an ERA or non-parenteral prostanoid) with symptomatic PAH were randomized (2:4:1) to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (tid), or riociguat capped at an exploratory dose of 1.5 mg tid. Patients who completed PATENT-1 were eligible to enter the PATENT-2 open-label extension in which all patients received riociguat individually adjusted to a maximum dose of 2.5 mg tid.[14] The primary endpoint in PATENT-2 was safety and tolerability.

Statistical analysis

Data for the overall pretreated group, and hemodynamic data for ERA-pretreated and prostanoid-pretreated subgroups have been presented previously.[15] Efficacy analyses compared the riociguat 2.5 mg–maximum tid and placebo groups in the subgroups of patients who had received background ERA or non-intravenous prostanoid treatment. ERA-pretreated patients were also stratified according to whether the duration of ERA pretreatment was three to six months (“early sequential combination therapy”) or >6 months (“long-term background ERA”). For 6MWD, analysis of covariance (ANCOVA) with baseline value as a covariate and treatment group and region as main effects was used to estimate least squares (LS) mean difference and 95% confidence interval (CI).

Data from the exploratory riociguat 1.5 mg tid dose group were excluded from this efficacy analysis, but the riociguat 1.5 mg tid and 2.5 mg tid dose groups were pooled for safety analysis. Two patients pretreated with both an ERA and a prostanoid were included in both the ERA-pretreated overall group and prostanoid-pretreated group for the primary efficacy analyses but excluded from the analysis of early sequential combination/long-term background ERA data.

Long-term safety was also evaluated for the above subgroups in PATENT-2, in which all patients, regardless of treatment assignment in PATENT-1, received riociguat 2.5 mg tid. All analyses were descriptive.

In PATENT-1, missing data were imputed as previously described.[12] For patients who stopped study medication prematurely, values recorded at the termination visit or last post-baseline visit were used. When a patient died or withdrew due to clinical worsening with no termination visit, the worst possible values were used for 6MWD (0 m),

Borg dyspnea score (10), EuroQoL Group 5-Dimensions Self-Report Questionnaire (EQ-5D) and Living with Pulmonary Hypertension (LPH) questionnaire. For World Health Organization functional class (WHO FC), a score of IV was used in the event of withdrawal due to clinical worsening with no termination visit, and a score of V was used in the event of death. For patients who completed the study as planned with no end-of-study efficacy measurement, the last post-baseline value was used. No imputation rules were used for pulmonary hemodynamics or *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the event of death or missing post-baseline data.

Results

Patients

In PATENT-1, 254 and 126 patients were randomized to riociguat 2.5 mg–maximum and placebo, respectively (Fig. 1a),[12] of whom 131 riociguat-treated and 60

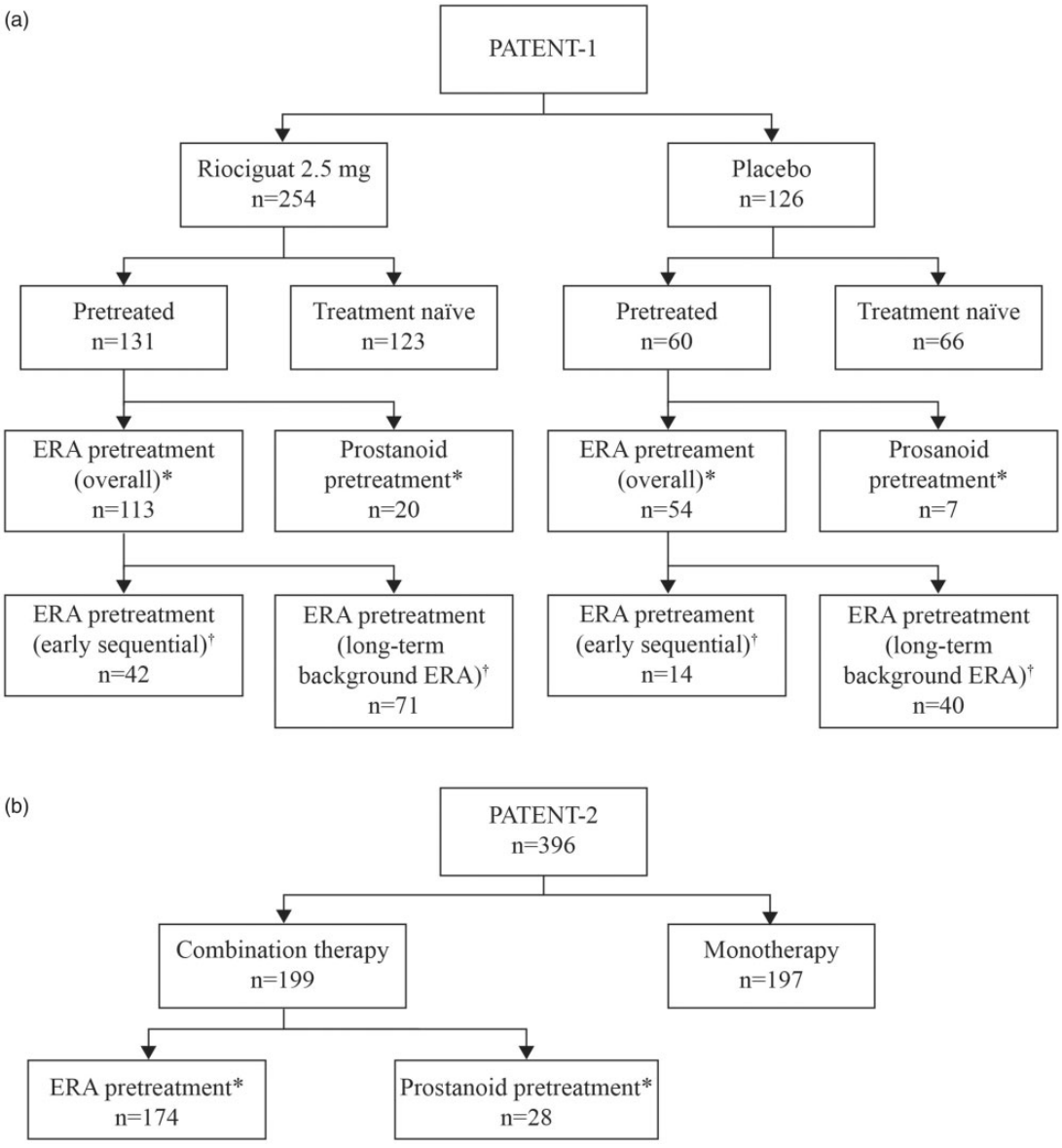

Fig. 1. Disposition of patients in the ERA-pretreated (overall, early sequential combination therapy, and long-term background ERA) and prostanoid-pretreated patients in (a) PATENT-1 and (b) PATENT-2.
*Two riociguat-treated patients and one placebo-treated patient received pretreatment with both an ERA and a prostanoid.
†Excludes patient pretreatment with both an ERA and a prostanoid.
ERA: endothelin receptor antagonist.
*Three patients were receiving combination therapy with both an ERA and a prostanoid.

placebo-treated patients were pretreated.[15] At PATENT-1 baseline, the mean (SD) durations of ERA pretreatment and prostanoid pretreatment were 581 (608) days (median [range]: 279 [2–2873]) and 356 (391) days (median [range]: 240 [24–1910]), respectively.

At the start of PATENT-2, 197 patients were receiving monotherapy and 199 patients were receiving combination therapy (Fig. 1b).[13] After two years, 123 patients were receiving riociguat monotherapy and 153 were receiving riociguat combination therapy. Of those patients starting PATENT-2 on riociguat monotherapy, 24 patients had progressed to receiving combination therapy with an ERA or prostanoid at this two-year time point. Baseline characteristics from PATENT-1 in ERA-pretreated patients (including the early sequential and long-term background ERA subgroups) and prostanoid-pretreated patients are shown in Table 1.

Efficacy outcomes

Early sequential and long-term background ERA groups. In the early sequential combination and long-term background ERA treatment groups in PATENT-1, mean ± SD 6MWD increased at Week 12 by + 22 ± 59 m ($N = 42$) and +23 ± 45 ($N = 71$), respectively, in the riociguat arm. In placebo-treated patients, mean ± SD 6MWD decreased by –42 ± 115 m in the early sequential group ($N = 14$) and increased by + 14 ± 64 m ($N = 40$) in the long-term background ERA group. The placebo-corrected mean treatment differences were +65 m (95% CI: 17 to 113 m) in the early sequential group and +13 m (95% CI: –8 to 33 m) in the long-term background ERA group. Riociguat treatment was associated with improvement or maintenance of WHO FC in a numerically greater percentage of patients than placebo (Fig. 2). In general, improvements in hemodynamics, NT-proBNP, quality of life (QoL) and Borg dyspnea score in the riociguat arm were numerically greater than those in the placebo arm (Table 2 and Table S1). Clinical worsening events in the early sequential group were experienced by one patient in the riociguat arm and two patients receiving placebo, and in the long-term background ERA group by one patient in the placebo arm (Table 3).

In PATENT-2, the mean ± SD change from baseline in 6MWD at two years was +30 ± 85 m in the early sequential combination group and +43 ± 67 m in the long-term background ERA group. At two years, WHO FC had improved in 43% and 35% of patients, respectively, was maintained in 57% and 53%, respectively, and deteriorated in 2% and 12%, respectively. Twenty-four patients (43%) in the early sequential group experienced clinical worsening events

Table 1. Baseline characteristics in PATENT-1 in ERA-pretreated patients (overall, receiving early sequential combination therapy, and on long-term background ERA therapy) and prostanoid-pretreated patients.

	Placebo				Riociguat 2.5 mg tid			
Parameter	Overall ERA pretreatment[a] ($N = 54$)	Early sequential ERA ($N = 14$)	Long-term background ERA ($N = 40$)	Prostanoid pre-treatment[a] ($N = 7$)	Overall ERA pretreatment[a] ($N = 113$)	Early sequential ERA ($N = 42$)	Long-term background ERA ($N = 71$)	Prostanoid pretreatment[a] ($N = 20$)
Age (years)	53 ± 15	53 ± 18	53 ± 15	52 ± 17	55 ± 15	55 ± 15	55 ± 15	50 ± 17
Female, n (%)	42 (78)	12 (86)	30 (75)	4 (57)	96 (85)	36 (86)	60 (85)	15 (75)
6MWD (m)	379 ± 64	363 ± 70	385 ± 61	355 ± 95	356 ± 69	348 ± 80	360 ± 62	334 ± 66
PVR (dyn·s·cm^{-5})	816 ± 496 ($N = 48$)	585 ± 306 ($N = 12$)	893 ± 526 ($N = 36$)	840 ± 263 ($N = 5$)	665 ± 367 ($N = 100$)	605 ± 312 ($N = 38$)	701 ± 395 ($N = 62$)	860 ± 348 ($N = 19$)
NT-proBNP (pg/ml)	1046 ± 1299 ($N = 46$)	1180 ± 845 ($N = 12$)	999 ± 1433 ($N = 34$)	2662 ± 3903	881 ± 1705 ($N = 98$)	773 ± 917 ($N = 35$)	942 ± 2019 ($N = 63$)	1223 ± 1079 ($N = 18$)
WHO FC I/II/III/IV (%)	0/43/55/2 ($N = 53$)	0/36/64/0	0/46/51/3 ($N = 39$)	0/29/71/0	1/33/66/1	0/29/71/0	1/35/62/1	10/30/60/0
EQ-5D score	0.7 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.2 ($N = 112$)	0.6 ± 0.3	0.7 ± 0.2 ($N = 70$)	0.6 ± 0.3
LPH score	41 ± 21 ($N = 51$)	38 ± 24 ($N = 13$)	42 ± 21 ($N = 38$)	54 ± 35	41 ± 20 ($N = 110$)	45 ± 21 ($N = 41$)	38 ± 20 ($N = 69$)	49 ± 23 ($N = 19$)
Borg dyspnea score[b]	4.5 ± 2.4	4.2 ± 2.7	4.7 ± 2.3	3.8 ± 2.5	4.6 ± 2.3	4.1 ± 2.3	4.8 ± 2.3	4.6 ± 2.3

Note: Data are mean ± standard deviation unless otherwise stated, and are for all patients in each subgroup unless individual Ns are specified in the table.
[a]Includes two riociguat-treated patient and one placebo-treated patient who received pretreatment with both an ERA and a prostanoid.
[b]After 6-minute walk test.
6MWD: 6-min walking distance; EQ-5D: EuroQol Group 5-Dimensions Self-Report Questionnaire; ERA: endothelin receptor antagonist; LPH: living with pulmonary hypertension questionnaire; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PVR: pulmonary vascular resistance; WHO FC: World Health Organization functional class.

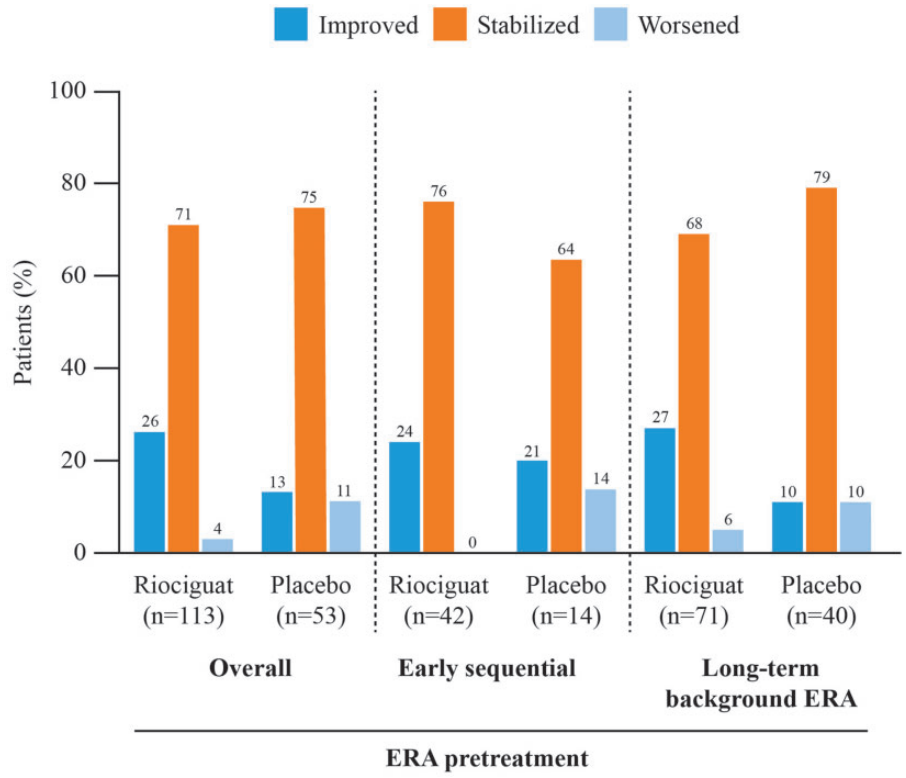

Fig. 2. Change from baseline in WHO FC at Week 12 in ERA-pretreated patients in the PATENT-1 study, overall, and in patients who received early sequential combination therapy or long-term background ERA.

Table 2. Summary of change from baseline at Week 12 in key hemodynamic endpoints in PATENT-1 in ERA-pretreated patients receiving early sequential combination therapy and on long-term background ERA.

	Placebo		Riociguat 2.5 mg tid	
Parameter	Early sequential ERA ($N=14$)	Long-term background ERA ($N=40$)	Early sequential ERA ($N=42$)	Long-term background ERA ($N=71$)
PVR (dyn·s·cm^{-5})	−3 ± 258	−60 ± 270	−158 ± 143	−184 ± 232
SVR (dyn·s·cm^{-5})	+92 ± 430	−141 ± 405	−380 ± 298	−361 ± 436
mPAP (mmHg)	−1 ± 5	−1 ± 6	−4 ± 7	−3 ± 7
MAP (mmHg)	+2 ± 11	−3 ± 13	−8 ± 13	−8 ± 11
RAP (mmHg)	+0 ± 4	−0.1 ± 3.8	+0 ± 4	−0.4 ± 4.0
Cardiac output (l/min)	−0.2 ± 1.3	+0.2 ± 0.7	+1.1 ± 1.0	+0.7 ± 1.0
Cardiac index (l/min/m^2)	−0.1 ± 0.7	+0.1 ± 0.4	+0.6 ± 0.5	+0.4 ± 0.6
SvO_2 (%)	−3.8 ± 12.6	−0.9 ± 5.3 [7]	+1.5 ± 7.7	+3.1 ± 7.5 [16]

Note: Data are mean ± standard deviation.
6MWD: 6-minute walking distance; ERA: endothelin receptor antagonist; MAP: mean arterial pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; SVR: systemic vascular resistance.

during two years of treatment (Table 4), with overall survival (95% CI) at two years of 97% (87 to 99%) (Fig. 3). In the long-term background ERA group, 33 patients (29%) experienced clinical worsening events and two-year overall survival was 92% (95% CI 85 to 96%).

Riociguat in combination with an ERA overall. In the overall group of ERA-pretreated patients in PATENT-1, the placebo-corrected change in 6MWD from baseline to Week 12 was +24 m (95% CI: 1 to 48 m),[12] and riociguat improved or maintained WHO FC in a numerically greater percentage

Table 3. Clinical worsening events in ERA-pretreated patients in PATENT-1.

	Placebo			Riociguat 2.5 mg tid		
Parameter, n (%)	Overall ERA pretreatment[a] ($N = 54$)	Early sequential ERA ($N = 14$)	Long-term background ERA ($N = 40$)	Overall ERA pretreatment[a] ($N = 113$)	Early sequential ERA ($N = 42$)	Long-term background ERA ($N = 71$)
Patients with clinical worsening	3 (6)	2 (14)	1 (3)	1 (1)	1 (2)	0 (0)
Hospitalization due to PH	3 (6)	2 (14)	1 (3)	1 (1)	1 (2)	0 (0)
Start of new PH treatment	2 (4)	1 (7)	1 (3)	1 (1)	1 (2)	0 (0)
Decrease in 6MWD due to PH	0 (0)	0 (0)	0 (0)	1 (1)	1 (2)	0 (0)
Persistent worsening of functional class due to PH	1 (2)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Death	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)

[a]Includes two riociguat-treated patients and one placebo-treated patient who received pretreatment with both an ERA and a prostanoid.
6MWD: 6-min walking distance; PH: pulmonary hypertension.

Table 4. Clinical worsening events in ERA-pretreated patients in PATENT-2.

	ERA pretreatment		
Parameter, n (%)	Overall ERA pretreatment[a] ($N = 174$)	Early sequential ERA ($N = 61$)	Long-term background ERA ($N = 113$)
Patients with clinical worsening	57 (33)	24 (39)	33 (29)
Heart/lung transplantation	2 (1)	2 (3)	0 (0)
Atrial septostomy	1 (1)	1 (2)	0 (0)
Hospitalization due to PH	25 (14)	9 (15)	16 (14)
Start of new PH treatment	33 (19)	12 (20)	21 (19)
Decrease in 6MWD due to PH	7 (4)	3 (5)	4 (4)
Persistent worsening of functional class due to PH	6 (3)	3 (5)	3 (3)
Death	31 (18)	13 (21)	18 (16)

[a]Includes two riociguat-treated patients and one placebo-treated patient who received pretreatment with both an ERA and a prostanoid.
6MWD: 6-min walking distance; PH: pulmonary hypertension.

of patients than placebo (Fig. 2). Data for mean change from baseline at Week 12 in pulmonary hemodynamics have been published previously,[15] and QoL and Borg dyspnea score data are shown in Table S1. Clinical worsening events were experienced by one patient (1%) in the riociguat arm and three patients (6%) receiving placebo (Table 3).

After two years of treatment in PATENT-2, mean ± SD change in 6MWD in patients pretreated with ERAs was +38 ± 76 m, while WHO FC was improved after two years in 39% of patients, maintained in 53%, and deteriorated in 8%. Clinical worsening events were reported by 57 patients (33%) during two years of treatment (Table 4).

Riociguat in combination with a prostanoid. In prostanoid-pretreated patients at PATENT-1 Week 12, 6MWD improved by a placebo-corrected change of + 106 m (95% CI: 38 to 173 m); however, it should be noted that 6MWD in this small subgroup was highly variable (range: –83 to + 279 m in the riociguat arm and –155 to + 48 m in the placebo arm). Further information on prostanoid-treated patients can be found in the online supplement, including Tables S1–3 and Fig. S1.

Safety

In PATENT-1, safety was similar between the treatment-naïve and pretreated subgroups.[15] In PATENT-2, adverse events (AEs) were experienced by the same proportion of patients in the treatment-naïve and pretreated subgroups (Table 5); however, the rate of AEs per 100 patient-years was higher in pretreated patients compared with treatment-naïve patients (Table 6 and Table S4) and discontinuations due to AEs and serious AEs (SAEs) were higher in pretreated patients compared with treatment-naïve patients (Table 5). Overall, long-term riociguat treatment was well

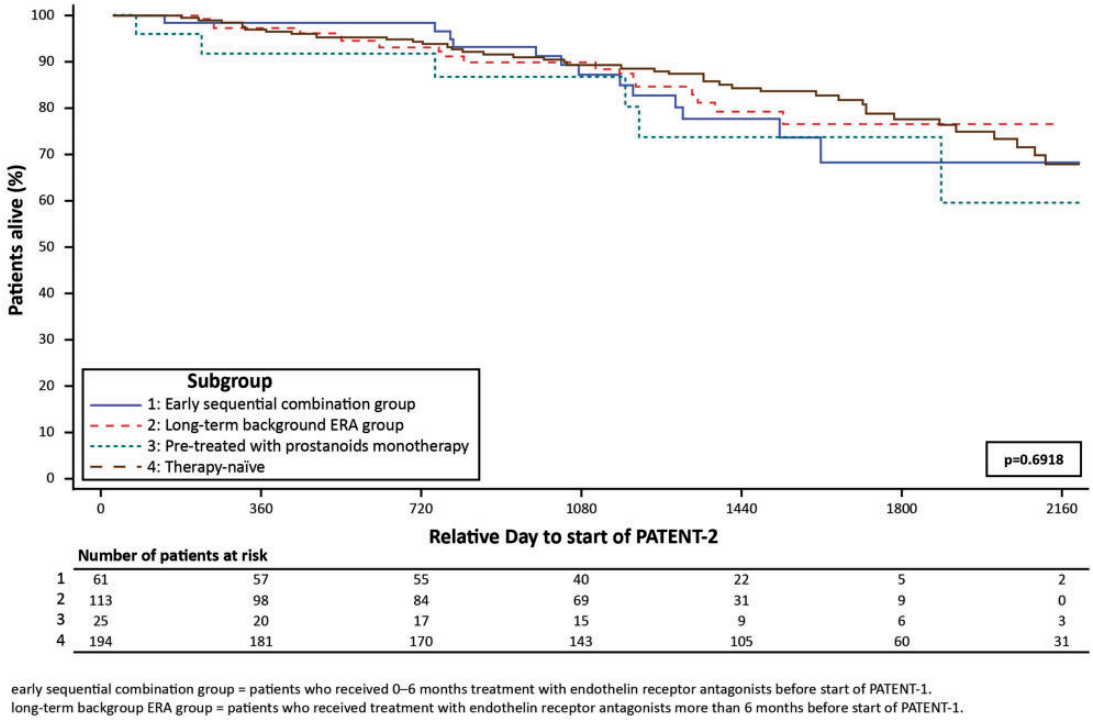

Fig. 3. Kaplan–Meier plot showing overall survival curves in PATENT-2 for patients in the 2.5 mg tid–maximum arm of PATENT-1. For patients who received placebo in PATENT-1, the start of PATENT-2 was considered to be Week 12, after patients had received four weeks of therapy at their optimum riociguat dose.

Table 5. Overall summary of safety in PATENT-2 in pretreated patients overall, ERA-pretreated patients (overall, receiving early sequential combination therapy, and on long-term background ERA), and in non-intravenous prostanoid-pretreated patients.

Events, n (%)	Treatment naïve (N = 197)	Any pretreatment (*N* = 199)	Overall ERA pretreatment[a] (*N* = 174)	Early sequential ERA (*N* = 61)	Long-term background ERA (*N* = 113)	Prostanoid pretreatment[a] (*N* = 28)
AEs	195 (99)	198 (99)	173 (99)	60 (98)	113 (100)	28 (100)
Discontinuations due to AEs	15 (8)	36 (18)	29 (17)	8 (13)	21 (19)	7 (25)
SAEs	125 (63)	145 (73)	127 (73)	51 (84)	76 (67)	21 (75)
Discontinuations due to SAEs	12 (6)	36 (18)	22 (13)	7 (11)	15 (13)	7 (25)
Deaths	38 (19)	30 (15)	26 (15)	10 (16)	16 (14)	5 (18)

[a]Includes two riociguat-treated patients and one placebo-treated patient who received pretreatment with both an ERA and a prostanoid.
AE: adverse event; ERA: endothelin receptor antagonist; SAE: serious adverse event.

tolerated in the combination therapy subgroups, with no new safety signals identified.

Discussion

The results of this analysis show that riociguat was associated with numerical improvements in exercise capacity, functional capacity, and hemodynamics after 12 weeks in patients who were pretreated with an ERA in the PATENT-1 study. Improvement in 6MWD was numerically greater in riociguat-treated patients in the early sequential than in long-term background ERA subgroups (LS mean differences: + 73 m and +13 m, respectively), suggesting that early sequential combination therapy with an ERA and riociguat is feasible and efficacious. As previously reported, the placebo-corrected change in 6MWD in ERA-treated patients overall was +24 m in PATENT-1.[15] The greatest improvement in 6MWD was observed in prostanoid-pretreated patients, although the small number of patients in this subgroup means that this result should be interpreted with caution.

Data from PATENT-2 show that improvements experienced with riociguat were sustained after two years of treatment, with improvement in 6MWD of + 30 m in the early

Table 6. Incidence per 100 person-years of the most common AEs ($\geq$ 10% of patients overall) in PATENT-2 in pretreated patients overall, ERA-pretreated patients (overall, receiving early sequential combination therapy, and on long-term background ERA) and in non-intravenous prostanoid-pretreated patients.

Events (rate per 100 person-years)	Treatment naïve ($N = 197$)	Any pretreatment ($N = 199$)	Overall ERA pretreatment[a] ($N = 174$)	Early sequential ERA ($N = 61$)	Long-term background ERA ($N = 113$)	Prostanoid pretreatment[a] ($N = 28$)
Any AE	2955 (378.4)	4028 (643.7)	3557 (650.4)	1311 (643.8)	2246 (654.3)	518 (606.0)
Headache	85 (10.9)	95 (15.2)	87 (15.9)	21 (10.3)	66 (19.2)	9 (10.5)
Peripheral edema	93 (11.9)	95 (15.2)	81 (14.8)	33 (16.2)	48 (14.0)	15 (17.6)
Dizziness	91 (11.7)	106 (16.9)	99 (18.1)	40 (19.6)	59 (17.2)	7 (8.2)
Nausea	38 (4.9)	76 (12.1)	70 (12.8)	22 (10.8)	48 (14.0)	6 (7.0)
Diarrhea	53 (6.8)	113 (18.1)	101 (18.5)	39 (19.2)	62 (18.1)	12 (14.0)
Dyspepsia	65 (8.3)	34 (5.4)	31 (5.7)	5 (2.5)	26 (7.6)	3 (3.5)
Nasopharyngitis	123 (15.8)	150 (24.0)	135 (24.7)	58 (28.5)	77 (22.4)	19 (22.2)
Dyspnea	38 (4.9)	66 (10.6)	55 (10.1)	24 (11.8)	31 (9.0)	11 (12.9)
Vomiting	36 (4.6)	65 (10.4)	62 (11.3)	22 (10.8)	40 (11.7)	3 (3.5)
Chest pain	38 (4.9)	41 (6.6)	34 (6.2)	17 (8.4)	17 (5.0)	7 (8.2)
Palpitations	23 (3.0)	28 (4.5)	25 (4.6)	7 (3.4)	18 (5.2)	3 (3.5)
Nasal congestion	7 (0.9)	13 (2.1)	13 (2.4)	3 (1.5)	10 (2.9)	0 (0)
Anemia	34 (4.4)	47 (7.5)	42 (7.7)	16 (7.9)	26 (7.6)	7 (8.2)
Gastroesophageal reflux disease	21 (2.7)	22 (3.5)	19 (3.5)	8 (3.9)	11 (3.2)	3 (3.5)
Hypotension	33 (4.2)	39 (6.2)	37 (6.8)	18 (8.8)	19 (5.5)	2 (2.3)
Hypokalemia	21 (2.7)	42 (6.7)	34 (6.2)	15 (7.4)	19 (5.5)	8 (9.4)
Cough	75 (9.6)	73 (11.7)	68 (12.4)	23 (11.3)	45 (13.1)	5 (5.9)
Respiratory tract infection	36 (4.6)	50 (8.0)	34 (6.2)	11 (5.4)	23 (6.7)	16 (18.7)
Urinary tract infection	16 (2.1)	37 (5.9)	36 (6.6)	15 (7.4)	21 (6.1)	1 (1.2)
INR increased	8 (1.0)	11 (1.8)	9 (1.7)	3 (1.5)	6 (1.8)	2 (2.3)
Musculoskeletal pain	7 (0.9)	18 (2.9)	17 (3.1)	10 (4.9)	7 (2.0)	1 (1.2)
Pruritus	7 (0.9)	15 (2.4)	13 (2.4)	7 (3.4)	6 (1.8)	2 (2.3)
Iron deficiency	8 (1.0)	18 (2.9)	18 (3.3)	7 (3.4)	11 (3.2)	0 (0)
Hepatic function abnormal	8 (1.0)	1 (0.2)	1 (0.2)	1 (0.5)	0 (0)	0 (0)

[a]Includes three patients who received pretreatment with both an ERA and a prostanoid.
AE: adverse event; ERA: endothelin receptor antagonist; INR: international normalized ratio; SAE: serious AE.

sequential group and +43 m in the long-term background ERA group (+38 m in patients pretreated with ERAs overall). Survival rates at two years were similar between the early sequential combination therapy and long-term background ERA subgroups (97%, and 92%, respectively), but were numerically lower in the prostanoid-pretreated subgroup (86%). It should be noted that the number of patients in this subgroup was small (25 patients at the start of PATENT-2, 17 patients at Day 720 (Fig. 3)). Furthermore, it is conceivable that the use of prostanoids as a first-line therapy in this subgroup may have preselected for a sicker population, despite the study entry criteria.

It is important that the efficacy of combination therapy is not outweighed by an intolerable increase in AEs. This analysis shows that long-term riociguat combination therapy was well tolerated in the early sequential combination and long-term ERA treatment subgroups in the PATENT studies, as well as in the prostanoid-treated subgroup, although overall, pretreated patients had higher rates of AEs per 100 patient-years and discontinuations due to AEs and SAEs compared with treatment-naïve patients. It should be noted, however, that pretreated patients tended to be sicker at PATENT-1 baseline (63% of pretreated patients were in WHO FC III/IV versus 43% of treatment-naïve),[15] and the increased pharmacological complexity of combination therapy may have potentially influenced AE rates. As in the present analysis, the most common AEs in PATENT and the CHEST study of riociguat in CTEPH were headache, dizziness, dyspepsia, and peripheral edema.[12,16] In the EXPERT registry of patients receiving riociguat, in which 79% of patients with PAH were receiving combination therapy (ERAs, 74%; prostanoids, 8%), riociguat was similarly well tolerated.[17]

Studies have indicated clear benefits of dual combination therapy targeting the endothelin and nitric oxide/cyclic

guanosine monophosphate pathways, and most patients with PAH at low or intermediate risk will benefit from dual combination therapy targeting these two pathways as standard care, either as upfront or early sequential combination therapy.[2] For example, data from the AMBITION study showed that the risk of clinical failure was reduced by 50% in treatment-naïve patients treated with ambrisentan and tadalafil in combination compared with either drug alone.[18] This exploratory analysis has allowed evaluation of patients who had only recently (within the previous three to six months) started ERA therapy before receiving riociguat, showing that early sequential combination therapy with an ERA plus riociguat was effective and well tolerated in this patient population. This is consistent with a recent report in which upfront combination therapy with riociguat and macitentan in patients with newly diagnosed PAH was associated with significant improvements in 6MWD, brain natriuretic peptide, and hemodynamic parameters.[19]

Limitations of the present analysis include its post hoc exploratory nature, and the limited patient numbers, particularly in the prostanoid group, with some outliers potentially biasing the data. There is no formal definition of "early sequential" combination therapy. The definition in the present study as starting within six months after start of first PAH-approved therapy was chosen as a balance between generating large enough subgroups for analysis and allowing time for patients to become stable on treatment, without being too long a period to qualify as "early". It should be noted that pretreated patients in PATENT-1 were required to be on stable background ERA for three months before entering the study.[12] Potential confounding factors when comparing different treatment strategies, such as longer disease duration in patients receiving long-term background ERA, must also be taken into consideration.

In conclusion, these data suggest that early sequential combination of an ERA plus riociguat is a feasible treatment option. Both early sequential combination therapy and long-term background ERA plus riociguat were well tolerated in the PATENT studies.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Supplemental Material

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References

1. Schermuly RT, Ghofrani HA, Wilkins MR, et al. Mechanisms of disease: pulmonary arterial hypertension. *Nat Rev Cardiol* 2011; 8: 443–455.
2. Galiè N, Humbert M, Vachiery JL, et al. 2015 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* 2015; 46: 903–975.
3. Humbert M and Ghofrani HA. The molecular targets of approved treatments for pulmonary arterial hypertension. *Thorax* 2016; 71: 73–83.
4. Lajoie AC, Bonnet S and Provencher S. Combination therapy in pulmonary arterial hypertension. *Pulm Circ* 2017; 7: 312–325.
5. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.
6. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
7. Gaine S and McLaughlin V. Pulmonary arterial hypertension: tailoring treatment to risk in the current era. *Eur Respir Rev* 2017; 26: 170095.
8. Fox BD, Shtraichman O, Langleben D, et al. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. *Can J Cardiol* 2016; 32: 1520–1530.
9. Lajoie AC, Lauziere G, Lega JC, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med* 2016; 4: 291–305.
10. Bayer AG. Adempas (Riociguat): EU Summary of Product Characteristics 2017, www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002737/WC500165034.pdf (accessed 2 April 2019).
11. Bayer AG. Adempas (Riociguat) US Prescribing Information 2017, http://labeling.bayerhealthcare.com/html/products/pi/Adempas_PI.pdf (accessed 2 April 2019).
12. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 330–340.
13. Ghofrani HA, Grimminger F, Grünig E, et al. Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial. *Lancet Respir Med* 2016; 4: 361–371.
14. Rubin LJ, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). *Eur Respir J* 2015; 45: 1303–1313.
15. Galiè N, Grimminger F, Grünig E, et al. Comparison of hemodynamic parameters in treatment-naïve and pre-treated patients with pulmonary arterial hypertension in the randomized phase III PATENT-1 study. *J Heart Lung Transplant* 2017; 36: 509–519.

16. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013; 369: 319–329.
17. Gall H, Ghofrani HA, Hoeper MM, et al. Riociguat for the treatment of pulmonary hypertension: safety data from the EXPERT registry. European Respiratory Society, London 2016. *Eur Respir J* 2016; PA2408.
18. Galiè N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
19. Sulica R, Sangli S, Chakravarti A, et al. Clinical and hemodynamic benefit of macitentan and riociguat upfront combination in patients with pulmonary arterial hypertension. *Pulm Circ* 2019; 9(1): 1–8.