ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

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ABSTRACT

BACKGROUND

Riociguat, a soluble guanylate cyclase stimulator, has been shown in a phase 2 trial to be beneficial in the treatment of pulmonary arterial hypertension.

METHODS

In this phase 3, double-blind study, we randomly assigned 443 patients with symptomatic pulmonary arterial hypertension to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). The 1.5 mg–maximum group was included for exploratory purposes, and the data from that group were analyzed descriptively. Patients who were receiving no other treatment for pulmonary arterial hypertension and patients who were receiving endothelin-receptor antagonists or (nonintravenous) prostanoids were eligible. The primary end point was the change from baseline to the end of week 12 in the distance walked in 6 minutes. Secondary end points included the change in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class, time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables, and safety.

RESULTS

By week 12, the 6-minute walk distance had increased by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; P<0.001). Prespecified subgroup analyses showed that riociguat improved the 6-minute walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance (P<0.001), NT-proBNP levels (P<0.001), WHO functional class (P=0.003), time to clinical worsening (P=0.005), and Borg dyspnea score (P=0.002). The most common serious adverse event in the placebo group and the 2.5 mg–maximum group was syncope (4% and 1%, respectively).

CONCLUSIONS

Riociguat significantly improved exercise capacity and secondary efficacy end points in patients with pulmonary arterial hypertension. (Funded by Bayer HealthCare; PATENT-1 and PATENT-2 ClinicalTrials.gov numbers, NCT00810693 and NCT00863681, respectively.)

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Pulmonary arterial hypertension is a life-threatening disease that is characterized by increased pulmonary vascular resistance owing to progressive vascular remodeling, which can ultimately lead to right heart failure and death.[1,2] Current treatments include phosphodiesterase type 5 inhibitors, prostanoids, and endothelin-receptor antagonists.[1] However, mortality remains high despite treatment,[3] and there is a considerable unmet medical need in the management of this disorder.

As noted elsewhere in this issue of the *Journal*,[4] riociguat is a member of a novel therapeutic class known as soluble guanylate cyclase stimulators. Riociguat has a dual mode of action, acting in synergy with endogenous nitric oxide and also directly stimulating soluble guanylate cyclase independently of nitric oxide availability.[5,6] In several phase 1 and 2 clinical studies, riociguat improved hemodynamic variables and exercise capacity in patients with pulmonary arterial hypertension.[5,7] We now present the results of the phase 3 Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1). In this study, we investigated the efficacy and side-effect profile of riociguat in patients with symptomatic pulmonary arterial hypertension, both those who were receiving no other treatment for the disease and those who were receiving treatment with endothelin-receptor antagonists or nonintravenous prostanoids.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted this 12-week, double-blind, randomized, placebo-controlled trial at 124 centers in 30 countries. The study was designed by the first author and the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) in collaboration with the sponsor, Bayer HealthCare. The institutional review board at each participating center approved the protocol. Data were collected according to Good Clinical Practice guidelines at the investigation sites. The steering committee had access to the complete database. The statistical analysis was performed by a statistician employed by the sponsor and was reviewed by the first author. All the drafts of the manuscript were prepared by the first author, and editorial assistance, funded by the sponsor, was provided by Adelphi Communications. The first author, with approval from the coauthors, made the decision to submit the manuscript for publication. The academic authors assume full responsibility for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of this report to the trial protocol, which is available at NEJM.org.

SELECTION OF PATIENTS

Patients with symptomatic pulmonary arterial hypertension (idiopathic, familial, or associated with connective-tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use) were included if they had a pulmonary vascular resistance greater than 300 dyn · sec · cm^{-5}, a mean pulmonary-artery pressure of at least 25 mm Hg, and a 6-minute walk distance of 150 to 450 m. Patients who were receiving no other treatment for pulmonary arterial hypertension and patients who were receiving treatment with endothelin-receptor antagonists or prostanoids (excluding intravenous prostanoids) at doses that had been stable for at least 90 days were eligible; patients who were receiving phosphodiesterase type 5 inhibitors were not eligible. Oral anticoagulant agents, as well as diuretics and supplemental oxygen at stable doses, were also permitted. Written informed consent was obtained from all the patients.

STUDY PROCEDURES

Eligible patients were randomly assigned, in a 2:4:1 ratio, to one of three regimens: placebo, oral riociguat administered in doses that were individually adjusted for each patient up to 2.5 mg three times daily (2.5 mg–maximum group), or oral riociguat administered in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). The dose-adjustment plan for riociguat is described in detail in Figure S1 and the section on the dosing regimen in the Supplementary Appendix. Riociguat therapy was initiated at a dose of 1 mg three times daily, and the dose was adjusted according to the patient's systolic systemic arterial blood pressure and signs or symptoms of hypotension (final range, 0.5 mg to 2.5 mg three times daily). The dose reached at the end of the 8-week adjustment phase was considered to be the appropriate dose for the patient, and the patient continued taking the drug at that dose for another 4 weeks. In the 1.5 mg–maximum group, therapy was initiated at a dose of 1 mg three times daily, and the dose was

adjusted every 2 weeks to a maximum dose of 1.5 mg three times daily. Since no further increase in dose was allowed, patients in this group and those in the placebo group underwent sham adjustment of doses to maintain the blinding of the treatment assignments. The 1.5 mg–maximum group was included for exploratory purposes, to provide information about lower riociguat doses, and data from that group were not included in the efficacy analyses.

Patients were seen at weeks 2, 4, 6, and 8 (during the dose-adjustment phase) and at week 12 (at the end of the maintenance phase). At each visit, clinical assessments and blood tests were performed. Patients who discontinued therapy for any reason were withdrawn from the trial; these patients underwent an efficacy assessment at the termination visit and had no further efficacy assessments after withdrawal. All surviving patients returned for a follow-up assessment of safety at 30 days. All patients who completed the 12-week PATENT-1 study period were eligible to enter the PATENT-2 long-term extension study.

OUTCOME MEASURES

The primary end point was the change from baseline to the end of week 12 in the distance walked in 6 minutes. Secondary efficacy end points included changes from baseline to the end of week 12 in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class (an adaptation of the New York Heart Association functional classification), the time to clinical worsening (as defined in the Supplementary Appendix), Borg dyspnea score (which ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea), score on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D, in which scores range from –0.6 to 1.0, with higher scores indicating better quality of life), and the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and higher scores indicating worse quality of life). Adverse events and laboratory variables were assessed throughout the study and during the safety follow-up period.

STATISTICAL ANALYSIS

We calculated that with 250 patients in the 2.5 mg–maximum group and 125 in the placebo group, the study would have 90% power to detect a least-squares mean difference in the 6-minute walk distance of 25 m, at a two-sided significance level of 5%. The primary efficacy analysis was performed on data from the modified intention-to-treat population (all patients who underwent randomization and received at least one dose of the study drug) (Fig. 1). A per-protocol analysis was also performed (see the Supplementary Appendix). Values that were missing owing to withdrawal of a patient from the study or death were imputed as described in the Supplementary Appendix.

The statistical analysis plan was identical to the plan in the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1).[4] Briefly, the primary end point and the secondary end points that were measured on a semicontinuous scale were analyzed by means of analysis of covariance followed by a test of normality of the residuals and, if rejected, a nonparametric stratified Wilcoxon test. Changes in the WHO functional class and the Borg dyspnea score were analyzed with the use of a stratified Wilcoxon test, and the time to clinical worsening was analyzed with the use of a stratified log-rank test. Secondary efficacy variables were tested with the use of a hierarchical testing procedure, in the following order: pulmonary vascular resistance, NT-proBNP level, WHO functional class, time to clinical worsening, score on the Borg dyspnea scale, EQ-5D score, and score on the LPH questionnaire (see the Supplementary Appendix). Safety was analyzed descriptively. Adverse events during the study period included all adverse events that started or worsened from the time of administration of the first dose of the study drug until 2 days after administration of the last dose. Further details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From December 2008 through February 2012, a total of 443 patients were randomly assigned to receive placebo (126 patients), riociguat at individually adjusted doses up to 2.5 mg three times daily (254 patients), or riociguat at individually adjusted doses capped at 1.5 mg three times daily (63 patients) (Fig. 1). The baseline characteris-

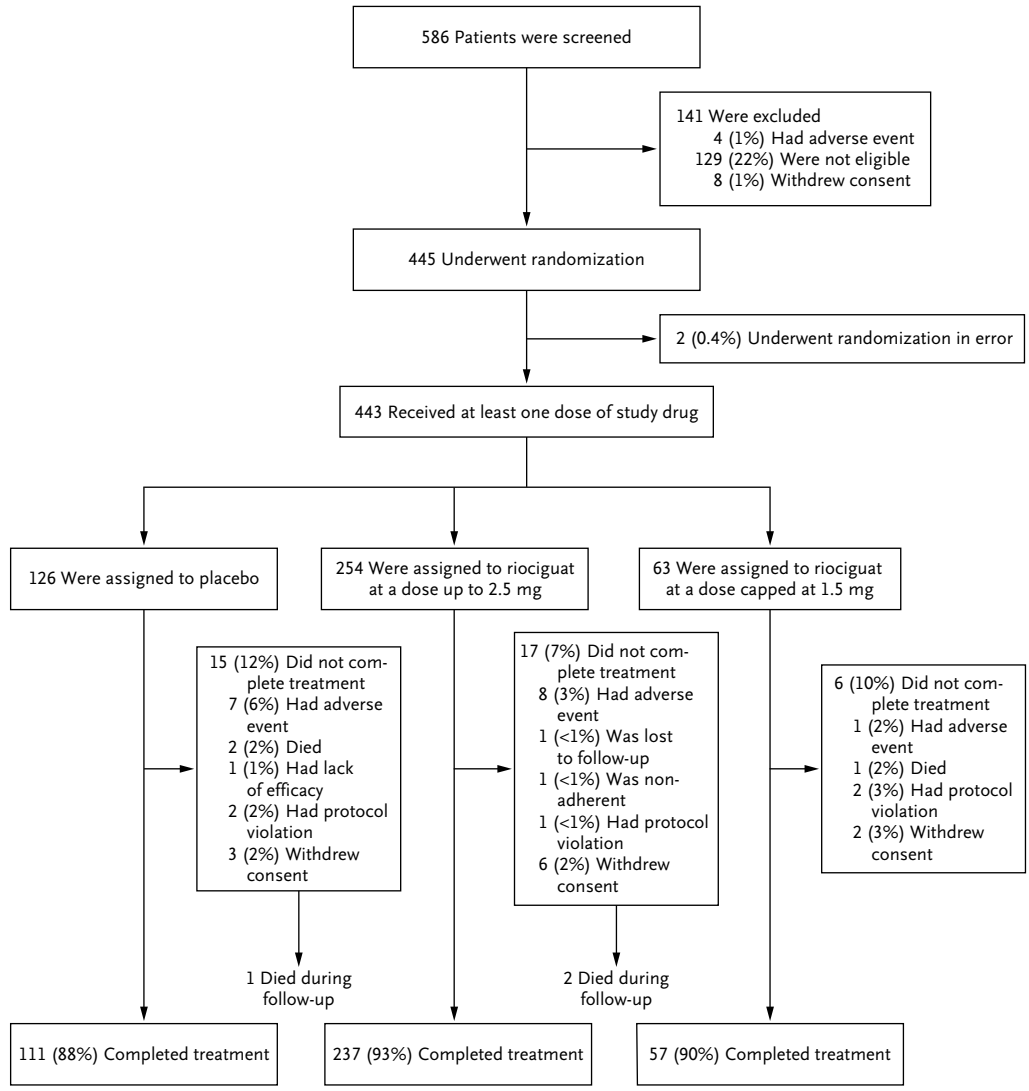

Figure 1. Screening, Randomization, and Follow-up.

The two patients who underwent randomization but did not receive a dose of the study drug (one in the placebo group and one in the 1.5 mg–maximum group) were ineligible for the study and were randomly assigned in error by the investigator. The three deaths during follow-up (two in the 2.5 mg–maximum group and one in the placebo group) occurred in patients who withdrew from the study and died during the 30-day follow-up period.

tics of the patients were well balanced among the groups (Table 1). Idiopathic pulmonary arterial hypertension was the most common diagnosis, and the majority of patients were in WHO functional class II or III. A total of 44% of the patients were receiving treatment with endothelin-receptor antagonists (primarily bosentan), and 6% were receiving prostanoid therapy (primarily inhaled iloprost); 50% were receiving no other treatment for pulmonary arterial hypertension. A total of 38 patients withdrew from the study before week 12 (Fig. 1).

DOSING

In the 2.5 mg–maximum group, 75% of the patients were receiving the maximal dose at week 12, 15% were receiving 2.0 mg three times daily, 6% 1.5 mg three times daily, 3% 1.0 mg three

times daily, and 2% 0.5 mg three times daily. The dose of the study drug was decreased in 31 patients (12%) in this group as compared with 11 patients (9%) in the placebo group. In the 1.5 mg–maximum group, 96% of the patients were receiving 1.5 mg three times daily at week 12.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N=126)	Riociguat, Maximum 2.5 mg 3 Times Daily (N=254)	Riociguat, Maximum 1.5 mg 3 Times Daily (N=63)	Total (N=443)
Female sex — no. (%)	98 (78)	203 (80)	49 (78)	350 (79)
Race — no. (%)†				
White	78 (62)	161 (63)	33 (52)	272 (61)
Black	1 (1)	4 (2)	1 (2)	6 (1)
Asian	38 (30)	79 (31)	22 (35)	139 (31)
Mixed	1 (1)	1 (<1)	0	2 (<1)
Not reported	8 (6)	9 (4)	7 (11)	24 (5)
Age — yr	51±17	51±17	49±16	51±17
Body-mass index‡	26±6	26±5	27±5	26±6
Pulmonary arterial hypertension classification — no. (%)				
Idiopathic	84 (67)	149 (59)	39 (62)	272 (61)
Familial	1 (1)	7 (3)	1 (2)	9 (2)
Associated with connective-tissue disease	25 (20)	71 (28)	15 (24)	111 (25)
Associated with congenital heart disease	12 (10)	15 (6)	8 (13)	35 (8)
Associated with portopulmonary hypertension	2 (2)	11 (4)	0	13 (3)
Associated with anorexigen or amphetamine use	2 (2)	1 (<1)	0	3 (1)
WHO functional class — no. (%)§				
I	4 (3)	5 (2)	5 (8)	14 (3)
II	60 (48)	108 (43)	19 (30)	187 (42)
III	58 (46)	140 (55)	39 (62)	237 (53)
IV	3 (2)	1 (<1)	0	4 (1)
Data missing	1 (1)	0	0	1 (<1)
Receipt of additional treatment for pulmonary arterial hypertension — no. (%)				
No	66 (52)	123 (48)	32 (51)	221 (50)
Yes¶	60 (48)	131 (52)	31 (49)	222 (50)
Endothelin-receptor antagonist	54 (43)	113 (44)	27 (43)	194 (44)
Prostanoid	6 (5)	18 (7)	4 (6)	28 (6)
6-Min walk distance — m	368±75	361±68	363±67	363±69

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the 2.5 mg–maximum group and the placebo group.
† Race was determined by the investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The World Health Organization (WHO) functional class ranges from I to IV, with higher numbers indicating greater functional limitations.
¶ Two patients in the 2.5 mg–maximum group and one in the placebo group were receiving both an endothelin-receptor antagonist and a prostanoid. For the analyses, these patients have been included in the endothelin-receptor–antagonist subgroup.º

PRIMARY END POINT

At week 12, the 6-minute walk distance had increased from baseline by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval [CI], 20 to 52; P<0.001), on the basis of an analysis of the modified intention-to-treat population with missing values imputed (Table 2 and Fig. 2). The benefit with riociguat was similar (Table S1 in the Supplementary Appendix) in sensitivity analyses for missing data that used statistical methods for longitudinal data, as described in the Supplementary Appendix. The increase in the 6-minute walk distance in the per-protocol population (Table S2 in the Supplementary Appendix) was consistent with the increase in the main analysis.

The treatment effect was consistent in several patient subgroups, including subgroups defined according to status with respect to treatment with additional agents for pulmonary arterial hypertension (Fig. S2 and Table S3 in the Supplementary Appendix). As anticipated, there was statistical evidence of heterogeneity of the treatment effect in subgroups defined according to WHO functional class; patients in functional class III or IV had a significantly greater benefit with riociguat therapy than did those in functional class I or II.

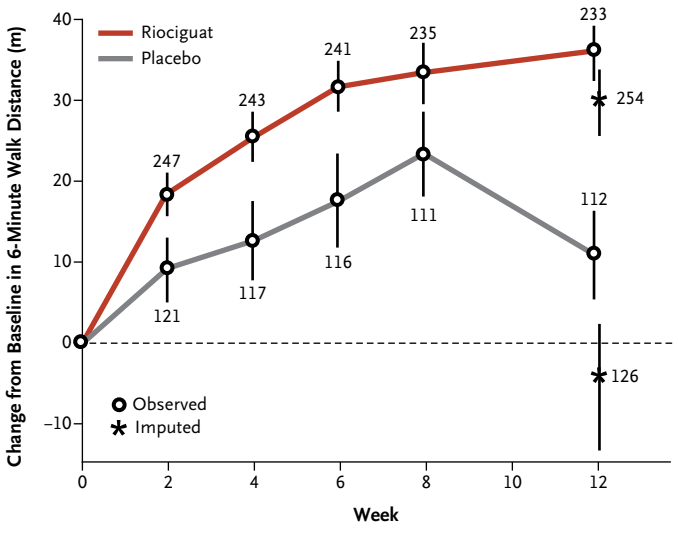

Figure 2. Mean Change from Baseline in the 6-Minute Walk Distance.
Mean (±SE) changes from baseline in the distance walked in 6 minutes during the 12-week PATENT-1 study period are shown in the group that received riociguat at a dose up to 2.5 mg three times daily as compared with the placebo group. The data were analyzed in the modified intention-to-treat population without imputation of missing values; imputed values are provided at week 12. The number at each data point indicates the number of patients included in the assessment at that time point. The least-squares mean difference in the 6-minute walk distance at week 12 was 36 m (95% CI, 20 to 52; P<0.001). The last observed value (not including follow-up) was carried forward for patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.

SECONDARY END POINTS IN THE 2.5 MG—MAXIMUM GROUP VERSUS THE PLACEBO GROUP

Pulmonary vascular resistance decreased by 223 dyn·sec·cm^{-5} in the 2.5 mg–maximum group, as compared with 9 dyn·sec·cm^{-5} in the placebo group (least-squares mean difference, –226 dyn·sec·cm^{-5}; 95% CI, –281 to –170; P<0.001) (Table 2). Significant improvements in other hemodynamic variables, including mean pulmonary-artery pressure and cardiac output, were also evident in patients treated with riociguat (Table 2). Significant benefits were seen in the 2.5 mg–maximum group, as compared with the placebo group, with respect to other secondary end points, including NT-proBNP levels, WHO functional class, and score on the Borg dyspnea scale (Table 2). There was also a significantly lower incidence of events indicating clinical worsening in the 2.5 mg–maximum group than in the placebo group (Table 3). The Kaplan–Meier estimates of the proportion of patients with clinical worsening are provided in Figure S3 in the Supplementary Appendix.

The EQ-5D score did not differ significantly between the 2.5 mg–maximum group and the placebo group (P=0.07). On the basis of the prespecified hierarchical testing procedure, the analysis of the scores on the LPH questionnaire was considered to be exploratory (Table S4 in the Supplementary Appendix); there was a nominally significant difference between the 2.5 mg–maximum group and the placebo group in that secondary outcome (Table 2).

END POINTS IN THE 1.5 MG—MAXIMUM GROUP

The analysis of the 1.5 mg–maximum group was exploratory, and data from that group were not included in the efficacy analyses. The results with respect to the primary and secondary end points in this group are shown in Table S5 in the Supplementary Appendix.

Table 2. Change from Baseline to End of Week 12 in Primary and Secondary End Points and Hemodynamic Variables.*

End Point	Placebo			Riociguat, Maximum 2.5 mg 3 Times Daily			Least-Squares Mean Difference (95% CI)	P Value†
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change		
Primary end point								
6-Min walk distance (m)‡	126	368±75	−6±86	254	361±68	30±66	36 (20 to 52)	<0.001
Secondary end points								
Pulmonary vascular resistance (dyn·sec·cm^{-5})	107	834±477	−9±317	232	791±453	−223±260	−226 (−281 to −170)	<0.001
NT-proBNP (pg/ml)	106	1228±1775	232±1011	228	1027±1799	−198±1721	−432 (−782 to −82)	<0.001
WHO functional class§	125	4 patients (3%) in class I, 60 (48%) in class II, 58 (46%) in class III, 3 (2%) in class IV	18 patients (14%) moved to lower class (indicating improvement), 89 (71%) stayed in same class, 18 (14%) moved to higher class	254	5 patients (2%) in class I, 108 (43%) in class II, 140 (55%) in class III, 1 (0.4%) in class IV	53 patients (21%) moved to lower class (indicating improvement), 192 (76%) stayed in same class, 9 (4%) moved to higher class	—	0.003
Borg dyspnea score¶	126	3.9±2.5	0.1±2.1	254	4±2	−0.4±1.7	—	0.002
EQ-5D score‖	124	0.7±0.2	−0.03±0.30	253	0.7±0.2	0.03±0.24	0.06 (0.01 to 0.11)	0.07
LPH score**	122	42±23	0.4±18.2	247	42±22	−6±18	−6 (−10 to −3)	0.002
Hemodynamic variables††								
Pulmonary-artery pressure (mm Hg)	109	49±15	−0.5±9.4	235	47±15	−4±8	−4 (−6 to −2)	<0.001
Mean arterial pressure (mm Hg)	109	91±12	−1±13	229	90±13	−9±11	−7 (−10 to −5)	<0.001
Right atrial pressure (mm Hg)	108	7±5	1±5	235	8±5	−0.2±5.8	−1.0 (−2.2 to 0.1)	0.07
Cardiac output (liters/min)	108	4±1	−0.01±1.07	233	4±1	1±1	0.9 (0.7 to 1.2)	<0.001
Pulmonary-capillary wedge pressure (mm Hg)	108	9±4	0.5±4.7	234	9±3	1±4	0.4 (−0.4 to 1.2)	0.08

Mixed venous oxygen saturation (%)	100	66±9	–2±9	210	65±10	3±8	5 (3 to 7)	<0.001
Heart rate (beats/min)	126	78±13	–0.4±11.0	254‡‡	76±11	0.8±10.7	—	—

* Plus–minus values are means ±SD. The changes from baseline to the end of week 12 are arithmetic means. The least-squares mean difference was calculated by analysis of covariance for the change from baseline to the last visit. NT-proBNP denotes N-terminal pro–brain natriuretic peptide.
† P values were calculated with the use of a stratified Wilcoxon test for the change from baseline to the last visit.
‡ The primary end point was analyzed in the modified intention-to-treat population as the change from baseline to the last observed value (not including follow-up) among patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.
§ The change in WHO functional class was analyzed with the use of a stratified Wilcoxon test.
¶ The Borg dyspnea scale ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea. The change in the Borg dyspnea score was analyzed with the use of a stratified Wilcoxon test; an analysis of covariance was not specified for this variable owing to the nonnormal distribution of the data.
‖ Scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) range from –0.6 to 1.0, with higher scores indicating better quality of life.
** Scores on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire) range from 0 to 105, with higher scores indicating worse quality of life. The analysis of this variable was an exploratory analysis owing to the hierarchical testing procedure.
†† All the analyses of hemodynamic variables were exploratory analyses, with the exception of heart rate, which was analyzed descriptively (and therefore has no P value associated with it).
‡‡ Data from 253 patients were available for the last visit.

SAFETY RESULTS IN THE 2.5 MG—MAXIMUM GROUP AND THE PLACEBO GROUP

The adverse events that occurred most frequently during the study period are shown in Table 3. The most frequently occurring serious adverse events were syncope (in 1% of the patients in the 2.5 mg–maximum group vs. 4% in the placebo group), worsening pulmonary hypertension (in <1% of the patients in the 2.5 mg–maximum group vs. 2% in the placebo group), chest pain (in 1% of the patients in both the 2.5 mg–maximum group and the placebo group), and right ventricular failure (in 1% of the patients in both groups). Drug-related serious adverse events in the 2.5 mg–maximum group included three cases of syncope (in 1% of the patients) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure, and hypotension (in a total of 0.4% of the patients), and in the placebo group, single cases of diarrhea, presyncope, syncope, dyspnea, and worsening pulmonary hypertension (in a total of 1% of the patients).

Eight patients (3%) in the 2.5 mg–maximum group and nine patients (7%) in the placebo group discontinued the study drug owing to adverse events. The following events leading to discontinuation of the study drug were considered by the investigator to be drug-related adverse or serious adverse events: in the 2.5 mg–maximum group, increased hepatic enzyme levels (serious), acute renal failure (serious), syncope (serious), esophageal pain and esophageal swelling, supraventricular tachycardia, hypotension, generalized edema, and neck pain; in the placebo group, diarrhea, syncope (serious), dyspnea, hypoxemia (serious), and worsening of pulmonary hypertension (serious). Deaths related to adverse events occurred in two patients (1%) in the 2.5 mg–maximum group (one each from sepsis and hemoptysis) and in three patients (2%) in the placebo group (one each from worsening anxiety followed by acute respiratory failure, worsening pulmonary hypertension, and respiratory failure); none of the deaths were considered to be related to the study drug.

LONG-TERM EXTENSION STUDY

A total of 396 patients (98% of the patients who completed the study) entered the long-term extension study PATENT-2, in which the treatment assignments were concealed for the first 8 weeks

Table 3. Clinical Worsening and Adverse Events.*

Event	Placebo (N=126)	Riociguat, Maximum 2.5 mg 3 Times Daily (N=254)	Riociguat, Maximum 1.5 mg 3 Times Daily (N=63)
	number of patients (percent)		
Clinical worsening			
All events	8 (6)	3 (1)†	2 (3)
Hospitalization due to pulmonary hypertension	4 (3)	1 (<1)	0
Start of new treatment for pulmonary hypertension	5 (4)	1 (<1)	1 (2)
Decrease in 6-min walk distance due to pulmonary hypertension	2 (2)	1 (<1)	1 (2)
Persistent worsening of WHO functional status due to pulmonary hypertension	1 (1)	0	0
Death	3 (2)	2 (1)	1 (2)
Adverse events			
Any	108 (86)	227 (89)	58 (92)
Headache	25 (20)	69 (27)	20 (32)
Dyspepsia	10 (8)	48 (19)	8 (13)
Peripheral edema	14 (11)	44 (17)	14 (22)
Nausea	16 (13)	40 (16)	10 (16)
Dizziness	15 (12)	40 (16)	15 (24)
Diarrhea	13 (10)	35 (14)	6 (10)
Vomiting	11 (9)	26 (10)	7 (11)
Nasopharyngitis	14 (11)	26 (10)	6 (10)
Hypotension	3 (2)	25 (10)‡	2 (3)
Anemia	3 (2)	21 (8)	1 (2)
Palpitations	6 (5)	20 (8)	5 (8)
Chest pain	11 (9)	18 (7)	4 (6)
Dyspnea	14 (11)	16 (6)	4 (6)
Gastroesophageal reflux disease	4 (3)	14 (6)	4 (6)
Cough	13 (10)	12 (5)	3 (5)
Nasal congestion	3 (2)	11 (4)	4 (6)
Tachycardia	7 (6)	9 (4)	0
Pyrexia	4 (3)	8 (3)	6 (10)
Fatigue	8 (6)	7 (3)	0
Chest discomfort	11 (9)	6 (2)	4 (6)
Flushing	7 (6)	5 (2)	2 (3)
Gastritis	0	4 (2)	4 (6)
Syncope	5 (4)	3 (1)	0

* The adverse events listed here are those that occurred in at least 5% of the patients in any group during the treatment period or up to 2 days after the end of treatment. The incidence of syncope as an adverse event of special interest is also reported.
† P=0.005 as compared with placebo, with the use of a stratified log-rank test.
‡ Of the 25 cases of hypotension reported in this group, 16 were mild, 8 were moderate, and 1 was severe.

and treatment was open-label thereafter. Of these patients, 363 patients (308 of whom were still receiving treatment at a median of 441 days) were included in an interim analysis of data collected up to April 2012. An exploratory analysis of the first 12 weeks of PATENT-2 showed further increases in the 6-minute walk distance in the 215 patients receiving up to 2.5 mg of riociguat three times daily. A mean (±SD) increase of 53±62 m over the baseline distance in PATENT-1 among these 215 patients was observed at week 12 of PATENT-2. The same group had had an increase of 36±54 m at week 12 of PATENT-1.

DISCUSSION

In this trial, riociguat significantly improved exercise capacity in patients with pulmonary arterial hypertension. This benefit was consistent in patients who were receiving endothelin-receptor antagonists or prostanoids and in those who were receiving no other treatment for the disease. Riociguat also significantly and consistently improved a range of secondary efficacy end points, including pulmonary hemodynamics, WHO functional class, and time to clinical worsening.

Although some studies suggest that the 6-minute walk distance has modest validity as a surrogate end point for clinical events,[8] it is the most frequently used primary end point in randomized, controlled trials involving patients with pulmonary arterial hypertension,[9] is an independent predictor of death,[10] and correlates with changes in functional status and hemodynamic variables and with survival.[11] The overall difference in the 6-minute walk distance with riociguat as compared with placebo (36 m) at 12 weeks is consistent with the increases observed in previous studies of other medications for the treatment of pulmonary arterial hypertension (16 to 59 m).[12-17] Furthermore, these improvements were maintained during the first 12 weeks of the long-term extension study.

The improvement in the 6-minute walk distance with riociguat as compared with placebo is also within the range of thresholds that have previously been reported to represent a clinically relevant change (31 to 42 m).[8,18,19] However, a large proportion of patients in PATENT-1 had WHO functional class II symptoms at baseline and a baseline 6-minute walk distance that was relatively long; thus, this population had less advanced illness than did the population in many previous studies. Indeed, there was statistical evidence from a subgroup analysis that WHO functional class influenced the beneficial effect of riociguat on the 6-minute walk distance — a finding that was anticipated from previous observations[13,15] — suggesting that the benefit with riociguat is more likely to be clinically important in patients with WHO functional class III or IV symptoms than in those with class I or II symptoms.

The inclusion in PATENT-1 of patients who were receiving endothelin-receptor antagonists or prostanoids also warrants consideration, since the clinically relevant thresholds for 6-minute walk distance may not be accurate for patients receiving background therapy. Another study, the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study,[15] closely resembled PATENT-1 with respect to both the patient population and the study design, since the PHIRST study included both patients who had received or were currently receiving no treatment for the disease and patients who were receiving endothelin-receptor antagonists. However, in the PHIRST study, patients receiving background endothelin-receptor–antagonist therapy did not have significant improvements in the 6-minute walk distance, whereas in PATENT-1, riociguat improved the 6-minute walk distance in both patients who were receiving no therapy for the disease and patients who were receiving endothelin-receptor antagonists or prostanoids.

In PATENT-1, riociguat was associated with consistent improvements across a range of clinically relevant primary and secondary end points, including 6-minute walk distance, pulmonary vascular resistance, and time to clinical worsening — improvements that were not seen in some previous trials. Delays in clinical worsening are considered to be clinically relevant,[20] and the delay in clinical worsening that was observed in PATENT-1 was consistent with the greater number of patients with improved or stable WHO functional class in the group receiving riociguat at a dose up to 2.5 mg three times daily than in the placebo group. The hemodynamic improvements observed with riociguat require further characterization but could be related to disease-modifying effects, such as antifibrotic, antiproliferative, and antiinflammatory effects, that were observed in preclinical

studies.[21-25] In addition, the increase in cardiac output was reflected by a decrease in NT-proBNP levels, which could be indicative of decreased right ventricular afterload.

An obvious limitation of PATENT-1 was the lack of follow-up efficacy measurements in patients who withdrew from the study. However, sensitivity analyses that were performed with a variety of approaches to impute missing data suggest that the results are dependable despite these losses to follow-up. Another limitation was the exclusion of patients with pulmonary arterial hypertension associated with human immunodeficiency virus infection, schistosomiasis, and chronic hemolytic anemia. Patients who were receiving treatment with phosphodiesterase type 5 inhibitors or intravenous prostanoids were also excluded from PATENT-1, and the effect of riociguat in such patients is unknown.

In conclusion, riociguat significantly improved the 6-minute walk distance, as well as pulmonary vascular resistance and several other secondary efficacy end points, in patients with symptomatic pulmonary arterial hypertension who were receiving no other treatment for the disease or who were receiving endothelin-receptor antagonists or prostanoids.

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