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Use of clinically relevant responder threshold criteria to evaluate the response to treatment in the Phase III PATENT-1 study

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KEYWORDS:
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treatment response;
responder threshold criteria

BACKGROUND: In PATENT-1, riociguat significantly improved 6-minute walking distance (6MWD) and a range of secondary end-points in patients with pulmonary arterial hypertension (PAH). We investigated whether riociguat increased the proportion of patients achieving clinically relevant responder thresholds compared with placebo during PATENT-1.

METHODS: In PATENT-1, a randomized, double-blind study, treatment-naïve patients or patients on background PAH-targeted therapy with symptomatic PAH received 12 weeks of treatment with placebo, riociguat up to 2.5 mg 3 times daily, or riociguat up to 1.5 mg 3 times daily. Increases in 6MWD $\geq$40 m, 6MWD $\geq$380 m, cardiac index $\geq$2.5 liter/min/m^2, mixed venous oxygen saturation $\geq$65%, World Health Organization functional class I/II, N-terminal pro-brain natriuretic peptide $<$1,800 pg/ml, and right atrial pressure $<$8 mm Hg were chosen as threshold criteria of a positive response.

RESULTS: Riociguat increased the proportion of treatment-naïve patients and patients on background PAH-targeted therapy with 6MWD $\geq$380 m at Week 12 (+21% and +15%, respectively), whereas there was a small reduction in 6MWD in placebo-treated patients for both sub-groups. Riociguat also increased the proportion of treatment-naïve patients and patients on background PAH-targeted therapy achieving World Health Organization functional class I/II (+12% and +19%, respectively) and cardiac index $\geq$2.5 liter/min/m^2 (+30% and +33%, respectively) at Week 12, whereas there was little change in the respective placebo groups.

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CONCLUSIONS: Compared with placebo, riociguat increased the proportion of treatment-naïve patients and patients on background PAH-targeted therapy who fulfilled criteria defining a positive response to therapy.
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In patients with pulmonary arterial hypertension (PAH), baseline evaluation enables physicians to determine the severity of disease and decide on the most appropriate treatment strategy. However, follow-up assessments are crucial for judging the response to treatment, and it is becoming apparent that they provide a more reliable prognostic estimation than a baseline evaluation alone.[1,2] Identifying and defining parameters that reflect clinical response and threshold values that correlate with survival are important goals for physicians managing patients with PAH. To this end, threshold criteria have been defined for several parameters in patients with PAH that correlate with survival and form part of the current recommended treatment goals.[1–3]

Riociguat, a novel soluble guanylate cyclase stimulator, is the first medical therapy to demonstrate robust efficacy consistently in 2 forms of pulmonary hypertension (PH), PAH and chronic thromboembolic PH.[4,5] In the pivotal Phase III PATENT-1 study, riociguat significantly improved 6-minute walking distance (6MWD) ($p < 0.001$) and a range of secondary end-points in patients with symptomatic PAH compared with placebo.[5] Based on the primary results of PATENT-1, we hypothesized that riociguat would increase the proportion of patients who achieved clinically relevant responder thresholds at the end of PATENT-1 compared with placebo. In this study, we present the proportion of patients achieving responder criteria for 6MWD, World Health Organization functional class (WHO FC), cardiac index, right atrial pressure (RAP), N-terminal prohormone brain natriuretic peptide (NT-proBNP), and mixed venous oxygen saturation (SvO_2) at baseline and at the end of the study.

Methods

Study design

The study design for PATENT-1 (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With Pulmonary Arterial Hypertension (PAH); ClinicalTrials.gov Identifier: NCT00810693), a multicenter, 12-week, double-blind, randomized, placebo-controlled study, has been published previously.[5] The study was carried out in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating centers, and all patients gave written informed consent.

Setting and participants

Full details of the inclusion and exclusion criteria for PATENT-1 have been published previously.[5] Briefly, patients with symptomatic PAH were eligible if they had pulmonary vascular resistance (PVR) >300 dyn · sec · cm^{-5}, mean pulmonary artery pressure ≥ 25 mm Hg, and 6MWD 150 to 450 m. Patients were either treatment-naïve with respect to PAH therapies or were receiving background therapy with endothelin receptor antagonists (ERAs) or non-intravenous prostanoids or both.

Randomization

Patients were randomly assigned in a 2:4:1 ratio to placebo, riociguat adjusted from a starting dose of 1 mg 3 times daily up to a maximum of 2.5 mg 3 times daily (riociguat 2.5 mg–maximum group); and riociguat adjusted from 1 mg 3 times daily up to a maximum of 1.5 mg 3 times daily (riociguat 1.5 mg–maximum group; exploratory group). Details of the dose-adjustment regimen have been published previously.[5]

Outcome measures

The primary efficacy outcome was the change from baseline at Week 12 in 6MWD. Secondary parameters relevant to this analysis included the change from baseline at Week 12 in PVR, NT-proBNP levels, and WHO FC. Exploratory outcomes included the change from baseline at Week 12 in a range of other hemodynamic parameters including SvO_2, RAP, and cardiac index.

Responder thresholds

As part of the original study protocol, the following pre-defined responder thresholds were evaluated for riociguat-treated and placebo-treated patients: increase in 6MWD $\geq$ 40 m, 6MWD $\geq$ 380 m, WHO FC I/II, cardiac index $\geq$ 2.5 liter/min/m^2, and SvO_2 $\geq$ 65%. The thresholds for 6MWD $\geq$ 380 m, cardiac index, SvO_2, WHO FC, and NT-proBNP are based on published prognostic levels.[2,3,6,7] The increase in 6MWD $\geq$ 40 m threshold is based on 2 publications that calculated the minimally important difference (the smallest change or difference in outcome measure, perceived as beneficial, that would justify a change in a patient's medical management) for 6MWD in patients with PAH.[8,9]

An additional post hoc analysis of these responder thresholds was performed for treatment-naïve patients and patients on background PAH-targeted therapy. The following responder thresholds did not form part of the original study protocol and were performed post hoc: NT-proBNP $<$ 1,800 pg/ml and RAP $<$ 8 mm Hg. These responder thresholds were evaluated for treatment-naïve patients and patients on background PAH-targeted therapy. The threshold value for RAP is based on current treatment guidelines that recommend normalization of right ventricular function.[1] The threshold value for NT-proBNP is based on a study that assessed the criteria for categorizing patients as stable/satisfactory or unstable/deteriorating.[2]

Analysis

The statistical analysis plan of PATENT-1 has been published previously.[5] The proportion of patients with responder thresholds at baseline and at Week 12 were analyzed descriptively and are reported for patients in the riociguat 2.5 mg–maximum group and the placebo group only, split by the treatment-naïve and background therapy sub-groups. Results for the background therapy sub-group are also presented split by pre-treatment with ERAs and with prostanoids. Data from the exploratory riociguat 1.5 mg–maximum group were not included in this analysis. Missing values for hemodynamic parameters and NT-proBNP, where the patient died or withdrew from the study, were imputed according to the last measurement obtained after baseline. For 6MWD and WHO FC, the last observed value was taken except in cases of death or clinical worsening without a termination visit, where worst values were imputed.

Results

Patients

In PATENT-1, 443 patients were randomly assigned and treated (riociguat 2.5 mg–maximum group, $n = 254$; riociguat 1.5 mg–maximum group, $n = 63$; and placebo, $n = 126$). At baseline, 221 (50%) patients were treatment-naïve, 194 (44%) were receiving prior treatment with ERAs, and 31 (7%) were receiving prior treatment with prostanoids. There were 3 patients receiving background therapy with both an ERA and a prostanoid, and these patients were included in both sub-groups for the purpose of these analyses.

Baseline demographics were well balanced across the sub-groups (Table 1). With regard to parameters used as responder thresholds, baseline values for 6MWD, PVR, cardiac index, and SvO_2 were comparable between treatment-naïve patients and patients on background PAH-targeted therapy (Table 1).

Dosing

In the riociguat group, 75% of patients were receiving the maximum dose of 2.5 mg 3 times daily at Week 12; 15% were receiving 2 mg 3 times daily, 6% were receiving 1.5 mg 3 times daily, 3% were receiving 1 mg 3 times daily, and 2% were receiving 0.5 mg 3 times daily.

6MWD

In the riociguat group, 49% of treatment-naïve patients and 37% of patients on background PAH-targeted therapy achieved an increase in 6MWD of $\geq$40 m at Week 12 compared with 20% and 27% of placebo-treated patients, respectively (Figure 1A and B). In patients on background PAH-targeted therapy, the response to riociguat was numerically greater in patients receiving background treatment with prostanoids (50%) compared with ERAs (35%) (Figure 1C and D).

In the riociguat group, there was an increase in the proportion of treatment-naïve patients (+21%) and patients on background PAH-targeted therapy (+15%) with 6MWD $\geq$380 m at Week 12 compared with a small decrease in the respective placebo-treated patients (−2% and −5%)

Table 1 Baseline Demographics and Clinical Characteristics for Treatment-Naïve Patients and Patients on Background PAH-Targeted Therapy in PATENT-1

Parameter	*n*	Treatment-naïve	*n*	Background therapy overall	*n*	Background therapy with ERAs	*n*	Background therapy with prostanoids
Age, years	221	48 (18)	222	53 (15)	194	54 (15)	31	50 (16)
Female	221	170 (77)	222	180 (81)	194	159 (82)	31	23 (74)
PAH classification	221		222		194		31	
Idiopathic		141 (64)		131 (59)		117 (60)		16 (52)
Familial		8 (4)		1 (<1)		0		1 (3)
CTD-associated PAH		41 (19)		70 (32)		60 (31)		11 (35)
CHD-associated PAH		20 (9)		15 (7)		12 (6)		3 (10)
Portal PH		10 (5)		3 (1)		3 (2)		0
Anorexigen/amphetamine-associated PAH		1 (<1)		2 (1)		2 (1)		0
6MWD, m	221	364 (71)	222	363 (68)	194	365 (67)	31	346 (73)
NT-proBNP, pg/ml	195	1,194 (1,841)	193	1,014 (1,634)	166	944 (1,531)	29	1,569 (2,126)
WHO FC I/II/III/IV	221	5/51/44/1	221	2/34/63/1	193	2/34/63/1	31	6/29/65/0
PVR, $dyn \cdot sec \cdot cm^{-5}$	200	882 (528)	197	739 (400)	173	724 (406)	27	846 (330)
mPAP, mm Hg	202	50 (16)	200	47 (14)	174	46 (14)	29	50 (13)
Cardiac index, liter/min/m^2	200	2.5 (0.7)	199	2.6 (0.6)	173	2.6 (0.6)	29	2.4 (0.6)
SvO_2, %	182	65 (10)	177	65 (8)	152	65 (8)	28	61 (9)
RAP, mm Hg	201	7.4 (4.8)	199	7.7 (5.1)	173	7.3 (4.2)	29	10.8 (8.4)

CHD, congenital heart disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; 6MWD, 6-minute walking distance; SvO_2, mixed venous oxygen saturation; WHO FC, World Health Organization functional class. Data are mean (SD) except for gender and PAH classification, n (%), and WHO FC, %.

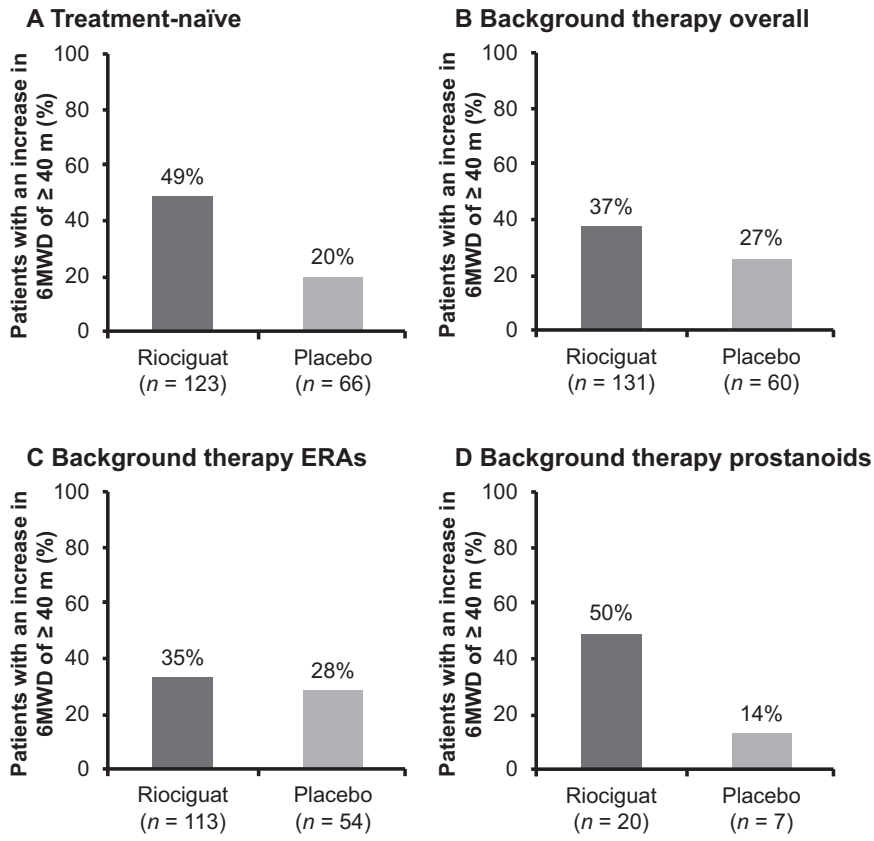

Figure 1 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) achieving an increase in 6-minute walking distance (6MWD) of ≥40 m at the end of PATENT-1. ERA, endothelin receptor antagonist.

(Figure 2A and B). In the riociguat group, a greater proportion of treatment-naïve patients (71%) achieved 6MWD ≥ 380 m than patients on background PAH-targeted therapy (56%). The response to riociguat was numerically greater in patients receiving background treatment with prostanoids (+25%) compared with ERAs (+13%) (Figure 2C and D).

World Health Organization functional class

In the riociguat group, there was an increase in the proportion of treatment-naïve patients (+12%) and patients on background PAH-targeted therapy (+19%) achieving WHO FC I/II at Week 12 (Figure 3A and B), whereas in the placebo group, there was little or no improvement from baseline in either sub-group (0% and +5%, respectively). Although the improvement appeared to be greater in patients on background PAH-targeted therapy, there was a greater proportion of treatment-naïve patients in WHO FC I/II (55%) at baseline compared with the background therapy sub-group (34%). The absolute percentage of patients achieving WHO FC I/II was greater in the treatment-naïve sub-group (67%) compared with the background therapy sub-group (53%). A similar response to riociguat was observed in patients receiving background treatment with prostanoids (+20%) and ERAs (+19%) (Figure 3C and D).

Cardiac index

In the riociguat group, 72% of treatment-naïve patients and 81% of patients on background PAH-targeted therapy (+30% and +33%, respectively) achieved a cardiac index of ≥2.5 liter/min/m^2 at Week 12 compared with 42% and 47% of placebo-treated patients (−2% and −6%, respectively) (Figure 4A and B). There was a numerically larger increase in the proportion of patients receiving background treatment with prostanoids (+45%) achieving this threshold compared with patients receiving background treatment with ERAs (+31%) (Figure 4C and D).

SvO_2

The proportion of treatment-naïve patients (+17%) and patients on background PAH-targeted therapy (+18%) with SvO_2 ≥ 65% was increased in the riociguat group, whereas treatment with placebo resulted in a notable decrease in both sub-groups at Week 12 (both −14%) (Figure 5A and B). A similar response to riociguat was observed in patients receiving background treatment with prostanoids (+20%) and ERAs (+17%) (Figure 5C and D). However, the absolute percentage of patients achieving this responder threshold was notably higher in the ERA sub-group (76%) compared with the prostanoid sub-group (45%).

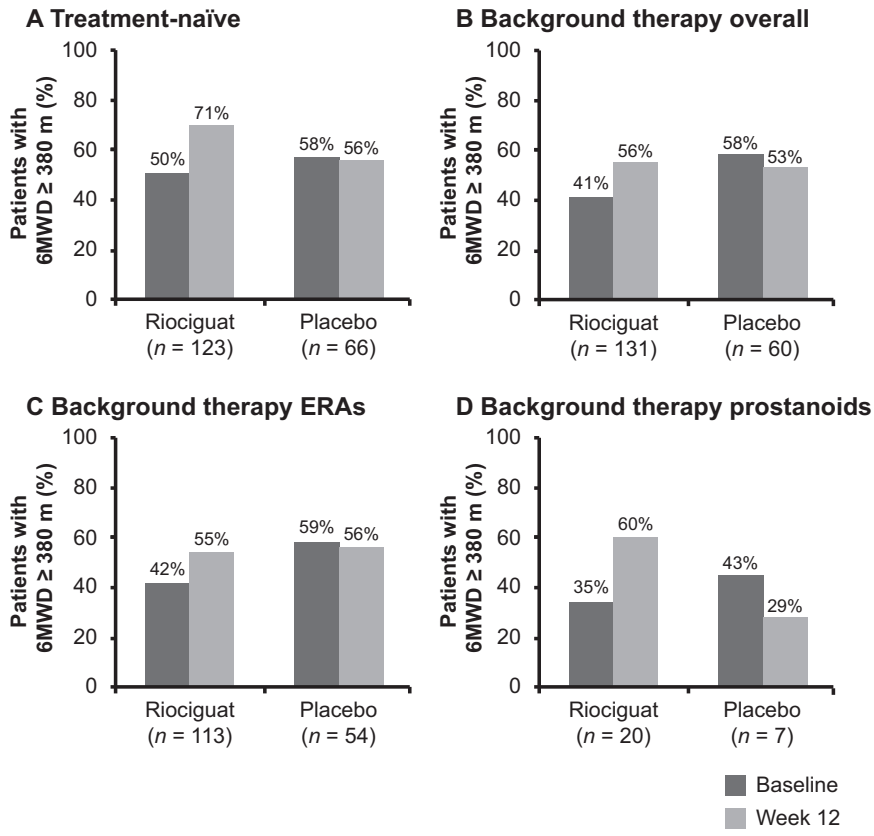

Figure 2 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with 6-minute walking distance (6MWD) $\geq$380 m at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

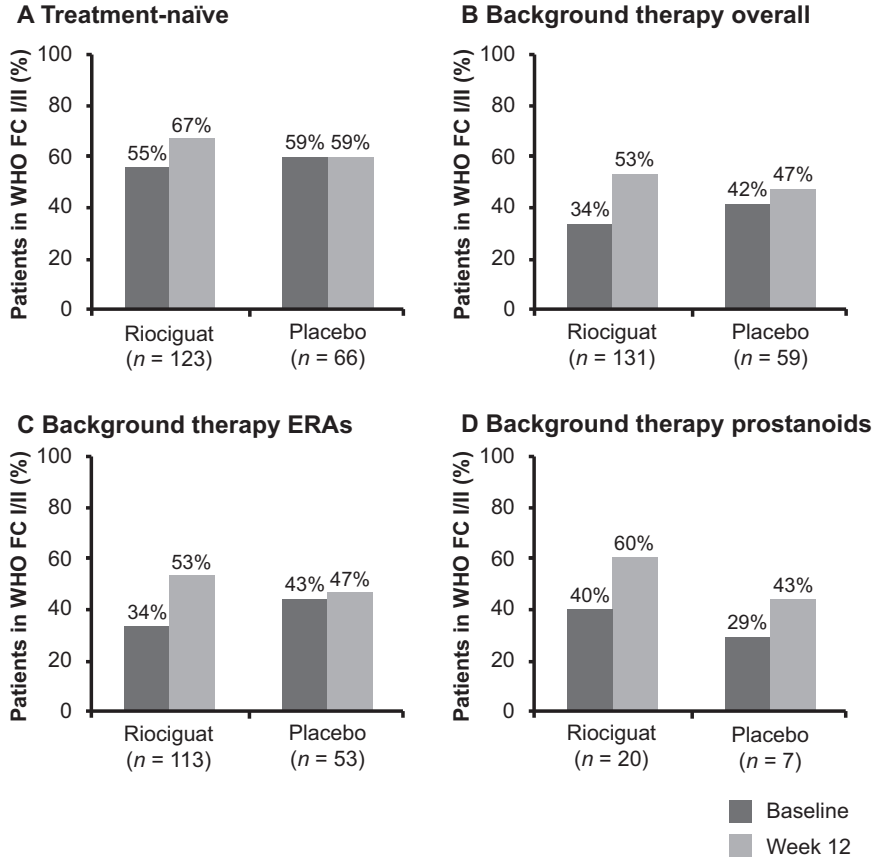

Figure 3 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with World Health Organization functional class (WHO FC I/II) status at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

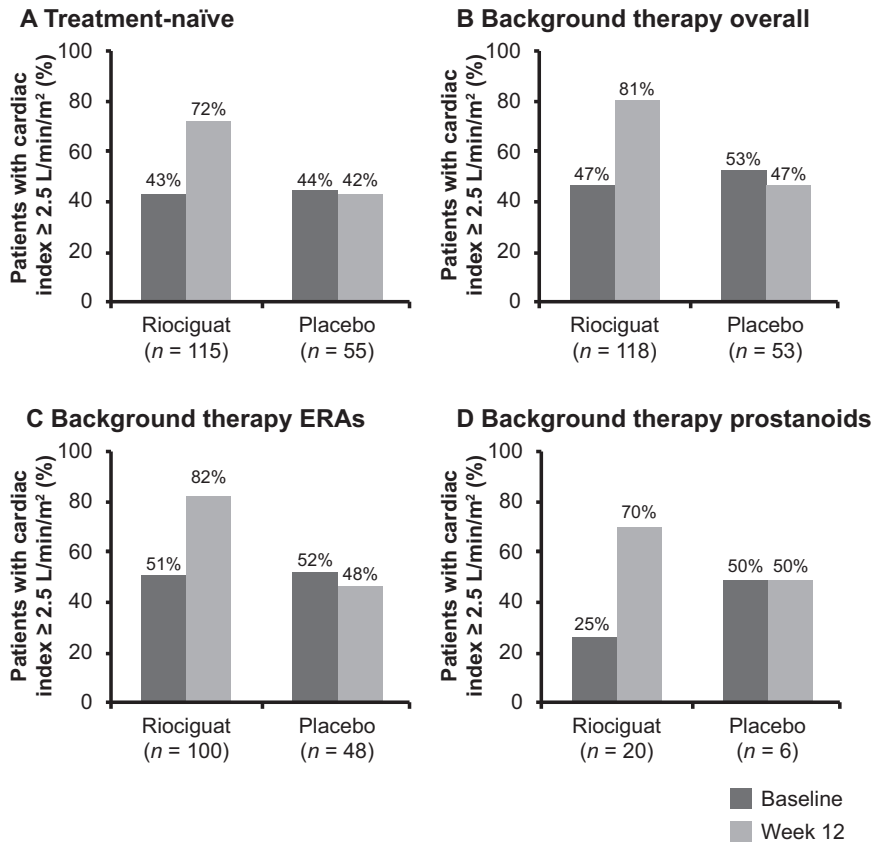

Figure 4 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with cardiac index $\geq$2.5 liter/min/m^2 at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

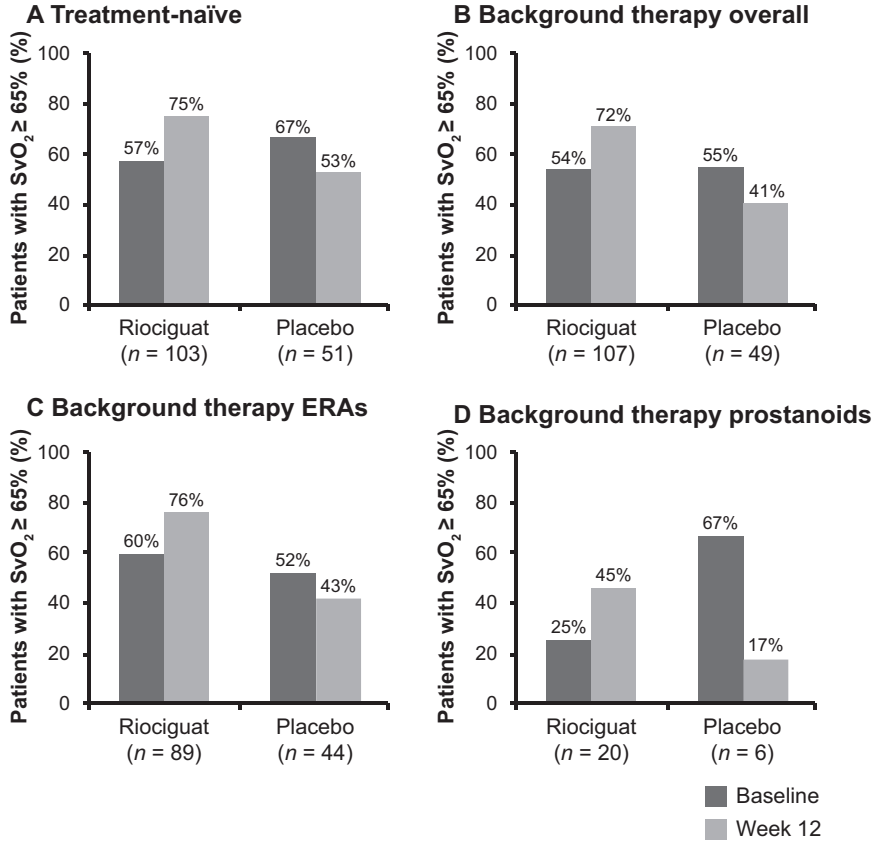

Figure 5 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with a mixed venous oxygen saturation (SvO_2) $\geq$65% at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

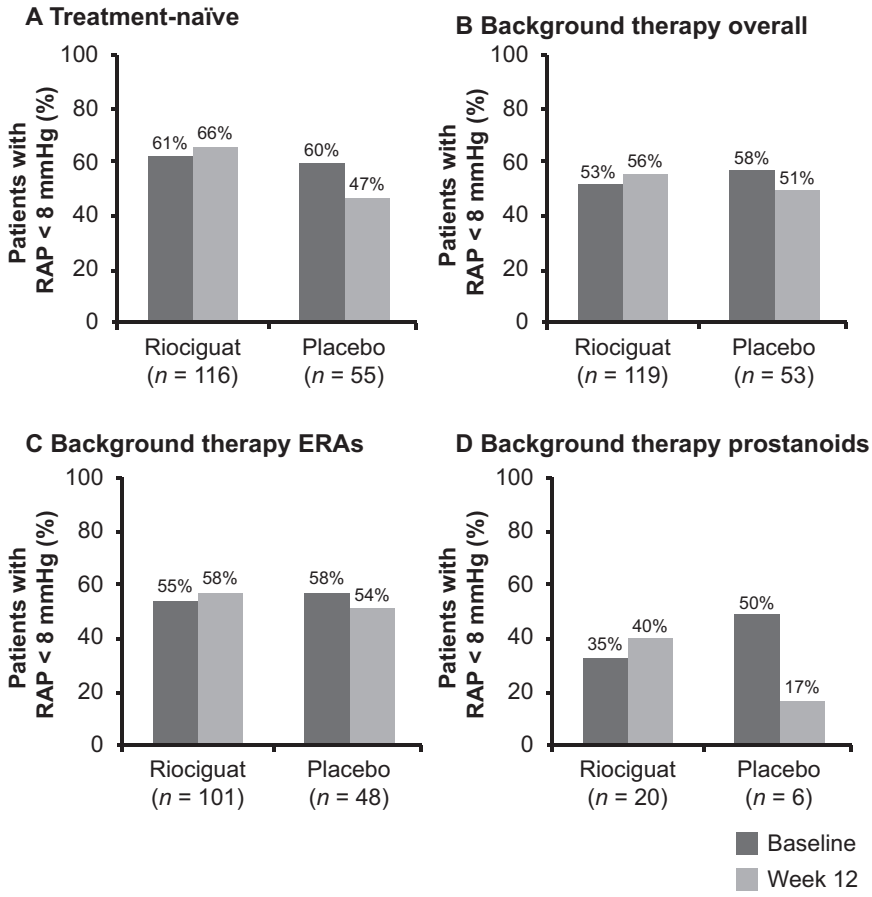

Figure 6 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with right atrial pressure (RAP) <8 mm Hg at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

RAP

In general, there was a small increase in the proportion of riociguat-treated patients achieving RAP < 8 mm Hg and a small decrease in the proportion of placebo-treated patients achieving this threshold in both sub-groups at Week 12 (Figure 6A–D).

NT-proBNP

There was a trend toward an increase in the proportion of riociguat-treated patients achieving NT-proBNP < 1,800 pg/ml in both sub-groups and a small decrease in the proportion of placebo-treated patients achieving this threshold at Week 12 (Figure 7A–C). The exception was in the prostanoid sub-group, where there was no difference in the proportion of riociguat-treated patients achieving this threshold at baseline and Week 12 (both 72%) compared with an increase (+14%) in the proportion of placebo-treated patients achieving this threshold at the end of PATENT-1 (Figure 7D).

Combined responder end-point

The proportion of patients with a combination of response criteria (6MWD ≥ 380 m, WHO FC I/II, cardiac index ≥2.5 liter/min/m^2, NT-proBNP < 1,800 pg/ml, and SvO_2 ≥65%) was 15% and 13% at baseline in the riociguat group (n = 193) and the placebo group (n = 93), respectively. After 12 weeks of treatment, the proportion increased to 34% in the riociguat group, whereas it was largely unchanged in the placebo group (16%).

Comparing the baseline demographics of patients achieving and not achieving this combined end-point at Week 12 (responders vs non-responders, respectively), responders appeared to be younger (mean age 44 vs 53 years), be in a lower WHO FC (4/73/23/0% vs 4/34/60/1% in WHO FC I/II/III/IV, respectively) and have a lower BMI (24 vs 27) compared with non-responders. The proportion of treatment-naïve patients was slightly higher in the responder group vs the non-responder group (58% vs 50%), but there were no differences in PAH sub-type between the 2 groups.

Safety

Safety data from PATENT-1 have been published previously.[5]

Discussion

Current treatment guidelines recommend analyzing multiple parameters for defining the success of therapy. There is no single test that can reliably serve as a long-term prognostic marker, and it is becoming increasingly apparent that

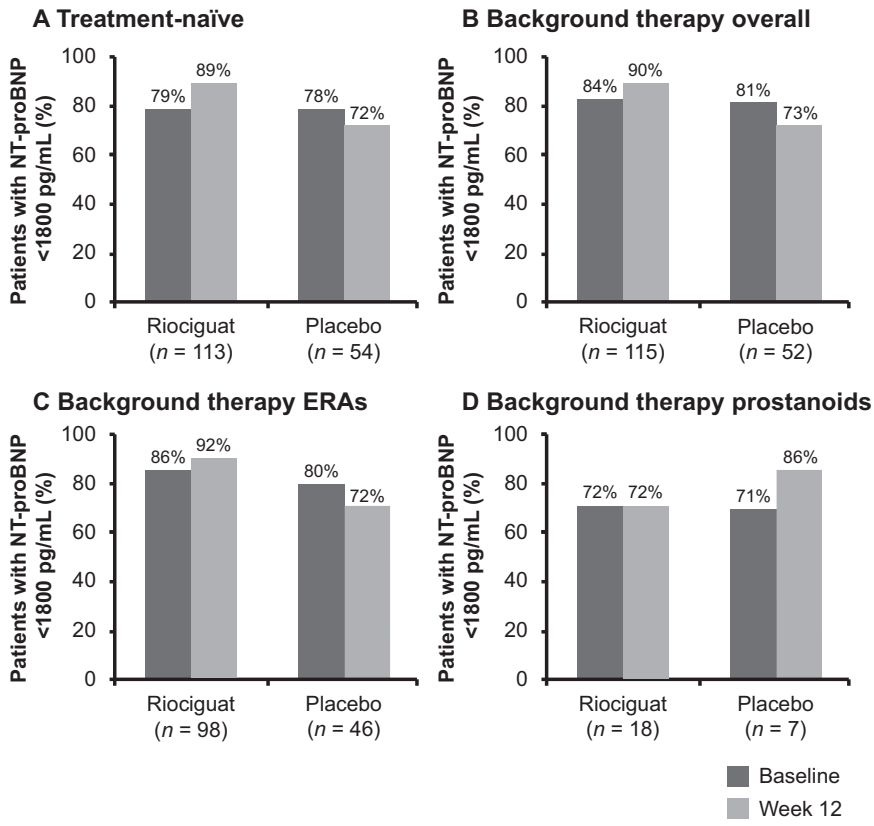

Figure 7 Proportion of treatment-naïve patients (A) and patients on background PAH-targeted therapy (B–D) with N-terminal prohormone brain natriuretic peptide (NT-proBNP) <1,800 pg/ml at baseline and at the end of PATENT-1. ERA, endothelin receptor antagonist.

composite treatment goals are more predictive of long-term outcome.[1] Revised treatment goals for patients with PAH have been published and include achievement of New York Heart Association FC I/II, 6MWD > 380 m, normalization of right ventricular size and function on echocardiography, a decreasing or normalization of brain natriuretic peptide or NT-proBNP, RAP < 8 mm Hg, and cardiac index >2.5 liter/min/m^2.[1,3] Current guidelines also recommend raising the threshold for some treatment goals, including 6MWD (from ≥ 380 to 440 m) and cardiac index (from >2.5 to 3 liter/min/m^2), to increase their prognostic relevance.[1] Several other responder criteria have also been defined in PAH registries and single-center studies, including NT-proBNP <1,800 pg/ml, SvO_2 ≥65%, 6MWD ≥380 m, 6MWD ≥ 440 m, brain natriuretic peptide <50 pg/ml, NT-proBNP <300 pg/ml, NT-proBNP >1,500 pg/ml, and percent predicted carbon monoxide diffusing capacity ≥80%.[2,10,11]

In PATENT-1, riociguat increased the proportion of patients achieving clinically relevant treatment goals for 6MWD, WHO FC, cardiac index, RAP, NT-proBNP, and SvO_2. The response to riociguat treatment, as assessed by these responder thresholds, was consistent in treatment-naïve patients and patients on background PAH-targeted therapy, underlining the demonstrated efficacy of riociguat as monotherapy and in combination with ERAs or non-intravenous prostanoids. The results support the positive primary data of PATENT-1 showing riociguat significantly improved 6MWD, PVR, NT-proBNP, WHO FC, time to clinical worsening, and Borg dyspnea score.[5] The improvement in multiple response criteria with riociguat highlights its efficacy in patients with symptomatic PAH.

The prognostic relevance of several responder criteria has been validated in previous studies. 6MWD has been evaluated as an indicator of survival in several studies, and different threshold values that correlate with improved survival have been reported.[7,11–14] Although the validity of 6MWD as a surrogate end-point for clinical events has been questioned by some studies, it is the most frequently used end-point in randomized, controlled trials for PAH and is viewed by the regulatory agencies as a clinically important end-point.[8,15–19] Nearly all available treatments for PAH have been approved for use based on an improvement in 6MWD. 6MWD is also an independent predictor of death and correlates with changes in functional class, with changes in hemodynamic variables, and with survival.[15,20] The responder threshold of 6MWD ≥ 380 m, as recommended by the European Society of Cardiology/European Respiratory Society 2009 guidelines,[3] is based on a study of 178 patients with primary PH in New York Heart Association functional class III/IV treated with epoprostenol, in which this threshold correlated with survival.[7] The 6MWD threshold value of an improvement ≥40 m was selected based on 2 publications that calculated the minimally important difference for 6MWD in patients with PAH as 33 m and 41.8 m.[8,9] In the present analysis, riociguat increased the proportion of patients with an absolute 6MWD value ≥380 m at Week 12 compared

with baseline; this was true for patients on background PAH-targeted therapy and treatment-naïve patients. In addition, riociguat-treated patients and placebo-treated patients in both sub-groups showed an increase in the proportion of patients with 6MWD $\geq$ 40 m at Week 12. This finding is in agreement with previously published observations in the overall placebo population that showed small increases in 6MWD during the time course of PATENT-1.[5] However, in both sub-groups, the proportion of riociguat-treated patients achieving this threshold was numerically greater compared with placebo-treated patients, although statistical significance testing was not conducted for this post hoc analysis.

Several studies, including the U.S. National Institutes of Health registry and REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management), demonstrated that patients in WHO FC I/II have improved survival compared with patients in WHO FC III/IV.[8,11,15–18] In addition, Nickel et al[2] showed that achieving WHO FC I/II after the initiation of targeted therapy is as important as disease severity at baseline in terms of predicting long-term outcomes. The present analyses demonstrate that riociguat treatment increased the proportion of patients achieving WHO FC I/II after 12 weeks of therapy, and this improvement was observed in treatment-naïve patients and patients on background PAH-targeted therapy.

Hemodynamic parameters have long been viewed as the "gold standard" when evaluating outcomes in patients with PAH.[1] The National Institutes of Health registry identified 3 hemodynamic parameters—RAP $\geq$ 20 mm Hg, mean pulmonary artery pressure $\geq$ 85 mm Hg, and cardiac index $<$2 liter/min/m^2—that were associated with an increased risk of death.[6] The correlation between mortality and right ventricular hemodynamic function has been confirmed in numerous studies, and RAP, cardiac index, and SvO_2 have been confirmed as independent prognostic factors.[1,2,11,12,14] However, the threshold value for cardiac index of $\geq$2.5 liter/min/m^2 is not based on clinical evidence but on this value being considered as the lower limit of normal in healthy subjects, and there is some debate on whether this value should be increased.[1] Short-term improvements in pulmonary hemodynamics, including cardiac output and PVR, were also found to be strongly predictive of long-term survival in patients with PAH from the Giessen Pulmonary Hypertension Registry.[21] The improvement in the responder criteria for these hemodynamic parameters in PATENT-1 may indicate a positive impact of riociguat on right ventricular function in patients with PAH and reinforce the value of right heart catheterization as a follow-up assessment.

NT-proBNP is an established biomarker of right ventricular dysfunction, and increased levels in patients with PAH are associated with poor clinical outcomes.[3] The NT-proBNP threshold of $<$1,800 pg/ml used by Nickel et al[2] is higher than previous cut-off values of 1,400 pg/ml and 1,500 pg/ml but was still shown to have prognostic value in patients with PAH; patients with NT-proBNP $<$1,800 pg/ml at baseline or after targeted therapy had better survival rates compared with patients with NT-proBNP levels $>$1,800 pg/ml.[2,11,22] The results of this analysis suggest that riociguat may improve right ventricular function; however, this would need to be confirmed using non-invasive imaging techniques such as echocardiography, Doppler imaging, and magnetic resonance imaging.

For some responder threshold criteria (increase in 6MWD $\geq$40 m at Week 12, 6MWD $\geq$380 m, and cardiac index $\geq$2.5 liter/min/m^2), a greater response to riociguat was observed in patients on background therapy with prostanoids compared with ERAs. Because of the small sample sizes of the sub-groups and exploratory nature of this analysis, further randomized studies are required before firm conclusions can be made. However, this observation could be attributed to differences in the baseline characteristics of the 2 patient sub-groups that show severity of the disease at baseline was greater in patients receiving background therapy with prostanoids compared with patients receiving background treatment with ERAs. The sub-group of patients receiving background therapy with prostanoids had greater scope for improvement with riociguat treatment. Another possibility is that the combination of riociguat and prostanoids has greater therapeutic potential, perhaps as a result of cyclic adenosine monophosphate/cyclic guanosine monophosphate crosstalk,[23] than the combination of riociguat and ERAs.

In addition to investigating single responder thresholds, we determined the number of patients achieving a combined responder end-point, including thresholds for 6MWD, WHO FC, cardiac index, NT-proBNP, and SvO_2. Riociguat increased the proportion of patients achieving this end-point compared with placebo. As expected, the proportion of patients achieving the combined end-point was lower than the proportion achieving individual criteria. The selection of thresholds for this combination of response criteria is arbitrary and based on the use of these parameters to guide goal-oriented treatment of PAH. The value of combined end-points in predicting long-term outcome so far has been shown only for validated equations such as the REVEAL risk score in patients with PAH.

The present study has several limitations. The responder thresholds of 6MWD $\geq$ 40 m, NT-proBNP $<$ 1,800 pg/ml, and SvO_2 $\geq$ 65% have not been validated in independent studies and do not form part of the current treatment goals for patients with PAH. Additionally, although the responder analyses were pre-planned for the total population, the analyses for the sub-groups were post hoc. These analyses are descriptive only, and firm conclusions regarding the significance of the observed differences are speculative only.

Analysis of the PATENT-2 study is required to establish whether the short-term improvements in these responder criteria are maintained with long-term riociguat treatment and if they correlate with improved outcomes for these patients. To this end, 1-year data from PATENT-2 have shown a good long-term safety profile, sustained improvements across several parameters, including 6WMD and WHO FC, and an overall survival rate at 1 year of 97% (L. J. Rubin et al, unpublished data, 2014).

In conclusion, this analysis of PATENT-1 demonstrates that riociguat treatment increases the proportion of patients achieving a range of clinically relevant responder threshold criteria. These improvements were consistent in treatment-naïve patients and patients receiving background therapy with ERAs or prostanoids, highlighting the consistent efficacy of riociguat in these different patient populations. The consistency of this treatment effect is further highlighted by the use of these responder criteria in the CHEST-1 patient population, which also demonstrated that riociguat treatment increased the proportion of patients achieving these responder thresholds.[24] Data from the ongoing long-term extension study, PATENT-2, are expected to help establish whether these responder criteria correlate with improved long-term outcomes.

Disclosure statement

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