Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial

Marius M Hoeper, Hikmet Al-Hiti, Raymond L Benza, Sung-A Chang, Paul A Corris, J Simon R Gibbs, Ekkehard Grünig, Pavel Jansa, James R Klinger, David Langleben, Vallerie V McLaughlin, Gisela M B Meyer, Jaquelina Ota-Arakaki, Andrew J Peacock, Tomás Pulido, Stephan Rosenkranz, Carmine Dario Vizza, Anton Vonk-Noordegraaf, R James White, Mikyung Chang, Frank Kleinjung, Christian Meier, Karen Paraschin, Hossein Ardeschir Ghofrani, Gérald Simonneau*; on behalf of the REPLACE investigators†*

Summary

Background Riociguat and phosphodiesterase-5 inhibitors (PDE5i), approved for the treatment of pulmonary arterial hypertension (PAH), act on the same pathway via different mechanisms. Riociguat might be an alternative option for patients with PAH who do not respond sufficiently to treatment with PDE5i, but comparisons of the potential benefits of riociguat and PDE5i in these patients are needed. The aim of this trial was to assess the effects of switching to riociguat from PDE5i therapy versus continued PDE5i therapy in patients with PAH at intermediate risk of 1-year mortality.

Methods Riociguat rEplacing PDE5i therapy evaLuated Against Continued PDE5i thErapy (REPLACE) was an open-label, randomised controlled trial in 81 hospital-based pulmonary hypertension centres in 22 countries. The study enrolled patients aged 18–75 years with symptomatic PAH at intermediate risk of 1-year mortality (based on the European Society for Cardiology–European Respiratory Society guideline thresholds for WHO functional class and 6-min walk distance [6MWD]) who were receiving treatment with a PDE5i with or without an endothelin receptor antagonist for at least 6 weeks before randomisation. Patients were excluded if they had been previously treated with riociguat, had used prostacyclin analogues or prostacyclin receptor agonists within 30 days before randomisation, had clinically significant restrictive or obstructive parenchymal lung disease, or had left heart disease. Patients were randomly assigned (1:1) to remain on PDE5i treatment (oral sildenafil [≥60 mg per day] or oral tadalafil [20–40 mg per day]; the PDE5i group) or to switch to oral riociguat (up to 2·5 mg three times per day; the riociguat group), using an interactive voice and web response system, stratified by cause of PAH. The primary endpoint was clinical improvement by week 24, defined as an absence of clinical worsening and prespecified improvements in at least two of three variables (6MWD, WHO functional class, and *N*-terminal prohormone of brain natriuretic peptide), analysed using last observation carried forward in all randomly assigned patients with observed values at baseline and week 24 who received at least one dose of study medication (the full analysis set). Secondary endpoints included clinical worsening events. The trial has been completed and is registered with ClinicalTrials.gov, NCT02891850.

Findings Between Jan 11, 2017, and July 31, 2019, 293 patients were screened, of which 226 patients were randomly assigned to the riociguat group (n=111) or to the PDE5i group (n=115). 211 patients completed the study and 14 patients discontinued (seven in each group). One patient assigned to the PDE5i group did not receive treatment, so 225 patients were included in the safety analysis, and one further patient in the PDE5i group had missing components of the composite primary endpoint at baseline, so 224 patients were included in the full analysis set. The primary endpoint was met by 45 (41%) of 111 patients in the riociguat group and 23 (20%) of 113 patients in the PDE5i group; odds ratio [OR] 2·78 (95% CI 1·53–5·06; p=0·0007). Clinical worsening events occurred in one (1%) of 111 patients in the riociguat group (hospitalisation due to worsening PAH) and 10 (9%) of 114 patients in the PDE5i group (hospitalisation due to worsening PAH [n=9]; disease progression [n=1]; OR 0·10 [0·01–0·73]; p=0·0047). The most frequently occurring adverse events were hypotension (15 [14%]), headache (14 [13%]), and dyspepsia (10 [9%]) in the riociguat group, and headache (eight [7%]), cough (seven [6%]), and upper respiratory tract infection (seven [6%]) in the PDE5i group. Serious adverse events were reported in eight (7%) of 111 patients in the riociguat group and 19 (17%) of 114 patients in the PDE5i group. During the study, four patients died in the PDE5i group, one of them during the safety follow-up period.

Interpretation Switching to riociguat from PDE5i treatment, both of which act via the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway, could be a strategic option for treatment escalation in patients with PAH at intermediate risk of 1-year mortality.

Lancet Respir Med 2021; 9: 573–84

Published Online March 24, 2021 https://doi.org/10.1016/S2213-2600(20)30532-4

See Comment page 546

*Joint senior authors

†For the full list of investigators see appendix

Clinic for Respiratory Medicine, Hannover Medical School, member of the German Center for Lung Research (DZL), Hannover, Germany (Prof M M Hoeper MD); Department of Cardiology, Institute of Clinical and Experimental Medicine-IKEM, Prague, Czech Republic (Prof H Al-Hiti MD); Division of Cardiovascular Diseases, Ohio State University, Columbus, OH, USA (Prof R L Benza MD); Division of Cardiology, Department of Medicine, Heart Vascular and Stroke Institute Imaging Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul, South Korea (Prof S-A Chang MD); Institute of Cellular Medicine, Newcastle University, Newcastle, UK (Prof P A Corris MD); National Heart and Lung Institute, Imperial College London, and Department of Cardiology, National Pulmonary Hypertension Service, Hammersmith Hospital, London, UK (J S R Gibbs MD); Centre for Pulmonary Hypertension, Thoraxklinik at Heidelberg University Hospital, Translational Lung Research Center (TLRC), member of DZL, Heidelberg, Germany (Prof E Grünig MD); 2nd Department of Medicine—Department of Cardiovascular

Medicine, First Faculty of Medicine, Charles University, and General University Hospital, Prague, Czech Republic (P Jansa MD); Division of Pulmonary, Sleep, and Critical Care Medicine, Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI, USA (Prof J R Klinger MD); Center for Pulmonary Vascular Disease and Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada (Prof D Langleben MD); Division of Cardiovascular Medicine, University of Michigan, Michigan Medicine, Ann Arbor, MI, USA (Prof V V McLaughlin MD); Centro de Hipertensão Pulmonar, Complexo Hospitalar Santa Casa de Porto Alegre, Porto Alegre, Brazil (Prof G M B Meyer MD); Pulmonary Circulation Group, Department of Medicine, Universidade Federal de São Paulo—Hospital São Paulo, São Paulo, Brazil (Prof J Ota-Arakaki MD); Scottish Pulmonary Vascular Unit, Regional Lung and Heart Centre, Glasgow, UK (Prof A Peacock MD); Cardiopulmonary Department, National Heart Institute, Mexico City, Mexico (Prof T Pulido MD); Clinic III for Internal Medicine (Cardiology), Cologne Cardiovascular Research Center (CCRC), and Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany (Prof S Rosenkranz MD); Pulmonary Hypertension Unit, Department of Cardiovascular and Respiratory Disease, La Sapienza University of Rome, Rome, Italy (Prof C D Vizza MD); Department of Pneumology, VU University Medical Center, Amsterdam, Netherlands (Prof A Vonk-Noordegraaf MD); University of Rochester Medical Center, Rochester, NY, USA (Prof R J White MD); Global Medical Affairs, Bayer AG, Berlin, Germany (M Chang MD, F Kleinjung PhD, C Meier MD); Bayer AG, São Paulo, Brazil (K Paraschin MD); University of Giessen and Marburg Lung Center, member of DZL, Giessen, Germany, Department of Pneumology, Kerchoff Clinic, Bad Nauheim, Germany, and Department of Medicine,

Funding Bayer AG, Merck Sharp & Dohme.

Introduction

Pulmonary arterial hypertension (PAH) is characterised by progressive pulmonary vascular remodelling that ultimately results in right-sided heart failure and death if not effectively treated. Currently approved therapies for PAH act via three distinct pathways: the endothelin pathway, the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway, and the prostacyclin pathway.[1] European Society of Cardiology–European Respiratory Society (ESC–ERS) guidelines for the treatment of PAH recommend a risk-based approach with the use of drug combinations to achieve a low-risk profile.[2–4] However, most patients (71–76%) with PAH do not reach a low-risk profile with contemporary treatments.[5–7]

Drugs approved for PAH that act via the NO–sGC–cGMP pathway include the phosphodiesterase-5 inhibitors (PDE5i) sildenafil and tadalafil, and the sGC stimulator riociguat. Although these two classes of drugs act via the same pathway, PDE5i and sGC stimulators have different modes of action. PDE5i block the degradation of cGMP; thus, the efficacy of these compounds depends on a functional NO–sGC–cGMP axis and the presence of intracellular cGMP.[8] Several lines of evidence suggest that this axis might be impaired in PAH, resulting in low intracellular cGMP levels, which potentially limits the clinical efficacy of PDE5i.[9] Further, in the presence of PDE5 inhibition, other phosphodiesterases could degrade cGMP, reducing the effect of PDE5i.[10] In contrast, riociguat increases intracellular cGMP levels by directly stimulating the sGC enzyme, independent of NO, and sensitising sGC to low intracellular NO concentrations.

The clinical relevance of these different modes of action is unclear. Sildenafil, tadalafil, and riociguat have received regulatory approval on the basis of randomised, placebo-controlled studies of 12–16-week durations, in which improved exercise capacity and improved haemodynamics were demonstrated.[11–13] Despite different study designs and inclusion criteria, the clinical effects of the three compounds appeared to be similar. However, as PAH is an orphan disease with low prevalence, studies directly comparing the safety and efficacy of PDE5i and riociguat have not been done.

As riociguat directly increases cGMP levels, it is possible that riociguat might be effective in patients not responding sufficiently to treatment with PDE5i. This hypothesis has been addressed in the Riociguat clinical Effects Studied in Patients with Insufficient Treatment response to PDE5 inhibitors (RESPITE) study.[14,15] RESPITE was an exploratory, uncontrolled, open-label, multicentre study. Eligible patients with PAH who had an

Research in context

Evidence before this study

We searched PubMed on Jan 15, 2016, using the search terms "pulmonary arterial hypertension" AND riociguat AND (transition OR switch) for clinical trials or case studies investigating the efficacy and safety of switching to riociguat in patients with pulmonary arterial hypertension (PAH) who, despite receiving treatment with phosphodiesterase-5 inhibitors (PDE5i), had not met their treatment goal. Very limited data were found, with only two case studies demonstrating initial improvement in clinical parameters when switching to riociguat from a PDE5i plus an endothelin receptor antagonist (ERA) or a PDE5i plus an ERA and a prostanoid. An updated search (on June 30, 2020) revealed eight additional case studies and, in 2017, results from the exploratory, uncontrolled, open-label, 24-week RESPITE study (n=61) demonstrated that patients with PAH who had an insufficient response to stable treatment with tadalafil or sildenafil showed improvements in 6-min walk distance, WHO functional class, *N*-terminal prohormone of brain natriuretic peptide concentration, and haemodynamic variables when switched to riociguat.

Added value of this study

To our knowledge, REPLACE was the first randomised trial to show a benefit when switching treatments in PAH that act within the same pathway, and the first head-to-head study suggesting a higher treatment response with riociguat versus PDE5i treatment. The results show that patients on a stable dose of PDE5i with or without an ERA, but still classified as at intermediate risk of 1-year mortality, according to European Society for Cardiology–European Respiratory Society treatment guidelines, can benefit from switching to riociguat compared with PDE5i maintenance therapy in terms of clinical improvement and risk status. No new safety signals were reported when patients were switched to riociguat, with data indicating a safety profile consistent with that previously observed for riociguat.

Implications of all the available evidence

The results of the open-label, randomised REPLACE trial are consistent with previous evidence from case studies and the uncontrolled RESPITE study of patients with PAH switched from a PDE5i to riociguat. Within the limitations of the PROBE (prospective, randomised, open-label, blinded endpoint) design, the totality of the evidence suggests that switching from a PDE5i to riociguat might be a strategic option for treatment escalation when aiming to achieve a low-risk status in patients with PAH.

insufficient response to a PDE5i-based treatment regimen (82% in combination with endothelin receptor antagonists [ERAs]) were switched from their respective PDE5i (sildenafil or tadalafil) to riociguat. Of the 61 patients enrolled, 51 completed the 24-week study period. Overall, these patients showed improvements in a range of endpoints, including exercise capacity, WHO functional class, cardiac biomarkers, and haemodynamic variables, and 16 (31%) of 51 patients met a predefined responder criterion (absence of clinical worsening, improvement from WHO functional class 3 to functional class 1 or 2, and improvement in 6-min walk distance [6MWD] ≥30 m).[15]

The results from RESPITE support the hypothesis that selected patients with PAH and an insufficient response to PDE5i might benefit from switching to riociguat. However, given the uncontrolled study design of RESPITE, further data were required to confirm the potential benefits seen. Therefore, we did a prospective, randomised controlled trial—the Riociguat rEplacing PDE5i therapy evaLuated Against Continued PDE5i thErapy (REPLACE) study—to assess the effect of switching to riociguat from PDE5i versus continuing PDE5i over 24 weeks in patients with PAH at intermediate risk of 1-year mortality.

Methods

Study design and participants

REPLACE was a prospective, open-label, randomised controlled trial conducted at 81 hospital-based pulmonary hypertension centres in 22 countries (appendix p 2).[16]

Men and women aged 18–75 years with symptomatic PAH, including idiopathic PAH, heritable PAH, drug-induced and toxin-induced PAH, PAH associated with congenital heart disease (PAH-CHD), portopulmonary hypertension (PoPH), or PAH associated with connective tissue disease (PAH-CTD), were enrolled. Patients were at intermediate risk of 1-year mortality, despite receiving stable doses of a PDE5i (oral tadalafil 20–40 mg per day or oral sildenafil ≥60 mg per day) as monotherapy or in combination with an ERA for at least 6 weeks before randomisation. Intermediate risk was defined as WHO functional class 3, with a 6MWD of 165–440 m at screening and randomisation, based on the thresholds from the ESC–ERS treatment guidelines.[2,3] Key exclusion criteria included previous treatment with riociguat, use of prostacyclin analogues or prostacyclin receptor agonists within 30 days before randomisation, clinically significant restrictive or obstructive parenchymal lung disease, and left heart disease. For full details of inclusion and exclusion criteria see the appendix (pp 6–9). All patients provided written informed consent. The institutional review board at each participating centre approved the protocol (appendix p 21), and the study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Randomisation and masking

Patients were enrolled by investigators at each study site. The randomisation schedule was generated by the Bayer randomisation group; patients were randomly assigned 1:1 to remain on PDE5i treatment (oral sildenafil [≥60 mg per day] or oral tadalafil [20–40 mg per day]; the PDE5i group) or to convert to oral riociguat (up to 2·5 mg three times per day; the riociguat group) centrally using an interactive voice and web response system (IxRS version 02; Almac, Craigavon, UK), and stratified by cause of PAH (idiopathic, heritable, or drug-induced and toxin-induced PAH; PAH-CHD or PoPH; or PAH-CTD). The randomisation group had no further involvement in the study. A mandatory 2-week screening period ensured clinical stability, absence of clinical deterioration, a stable dose of concomitant medications (eg, diuretics), and similar starting conditions for patients at the time of randomisation.

Given the variability in global PDE5i prescription patterns and associated complexity in study conduct, the study was open-label with no masking of treatment assignment. However, masked assessment of 6MWD and WHO functional class was done as part of the study protocol, with assessments made by a site-identified physician or nurse who did not know the treatment assignment, was not involved in the process of study drug administration, and was unaware of immediate blood pressure or heart rate effects after dosing. Compliance with this masking was assessed during routine monitoring visits (by an assigned monitor). *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) was assessed and recorded at a central laboratory. In addition, independent, masked central adjudication was done by the Clinical Endpoint Committee for the primary endpoint, hospitalisation events (ie, hospitalisation due to worsening PAH), and disease progression (appendix p 9).

Procedures

The study consisted of a 14-day screening period, 24 weeks of randomised treatment, and a 30-day safety follow-up period. Patients in the riociguat group had a PDE5i washout period of 24 h when receiving sildenafil and 48 h when receiving tadalafil at the time of randomisation. Oral riociguat (Bayer AG, Kaiser-Wilhelm-Allee, Leverkusen, Germany) was administered according to the established dose-adjustment scheme, beginning at 1 mg three times per day, and adjusted up to a maximum dose of 2·5 mg three times per day over an 8-week period. Following the dose-adjustment period, patients received riociguat for an additional 16 weeks. Patients in the PDE5i group continued their current treatment with oral sildenafil (≥60 mg per day; Pfizer, New York, NY, USA) or oral tadalafil (20–40 mg per day; Eli Lily, Indianapolis, IN, USA) for 24 weeks. Patients taking combination therapy with an ERA at baseline continued, regardless of study randomisation.

Imperial College London, London, UK
(Prof H-A Ghofrani MD); **and Assistance Publique–Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Saclay, Laboratoire d'Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and Inserm U999, Le Kremlin-Bicêtre, France**
(Prof G Simonneau MD)

Correspondence to:
Prof Marius M Hoeper, Clinic for Respiratory Medicine, Hannover Medical School, member of DZL, 30625 Hannover, Germany
Hoeper.Marius@mh-hannover.de

See **Online** for appendix

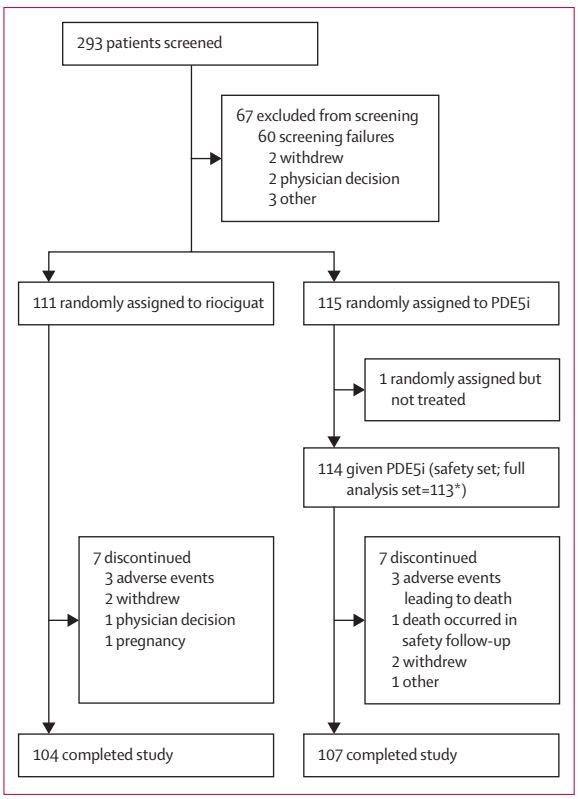

Figure 1: **Trial profile**
Includes the 24-week treatment period and 30-day safety follow-up. PDE5i=phosphodiesterase-5 inhibitor. *One patient had missing components of the primary endpoint at baseline.

The study protocol allowed for treatment escalation in either group, at any time, ensuring alignment with treatment guidelines. The decision to escalate treatment was at the discretion of the investigator.

Study visits took place at screening, baseline, and weeks 8, 16, and 24. Baseline measurements were done at randomisation while patients were still receiving PDE5i. 6MWD, WHO functional class, and NT-proBNP, were assessed at every visit. PAH risk scores (measured with the Registry to Evaluate Early and Long-Term PAH Disease Management [REVEAL] risk score, the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [COMPERA] score, and the French Pulmonary Hypertension Network [FPHN] non-invasive risk score) were evaluated at baseline and at weeks 16 and 24.[6,7,17] Adverse events and other safety outcomes were evaluated throughout the study and at the 30-day safety follow-up.

Outcomes

The centrally adjudicated primary efficacy endpoint was a composite endpoint of clinical improvement in at least two of the following criteria: 6MWD increase by 10% or more or 30 m or more from baseline to week 24, WHO functional class 1 or 2 at week 24, or NT-proBNP concentration reduction of 30% or more from baseline to week 24, in the absence of clinical worsening. The primary endpoint was assessed in several prespecified subgroups, stratified by age (<65 *vs* ≥65 years), sex, baseline 6MWD (<320 m *vs* ≥320 m), PAH subtype (idiopathic PAH, hereditary PAH, or drug-induced and toxin-induced PAH; PAH-CHD or PoPH; or PAH-CTD), baseline treatment with PDE5i combination therapy with an ERA versus monotherapy, baseline treatment with sildenafil versus tadalafil, and baseline ERA treatment subgroup (bosentan, ambrisentan, and macitentan).

Clinical worsening was defined as death from any cause, hospitalisation for worsening PAH (non-elective hospitalisation due to PAH or initiation of parenteral prostanoid therapy), or disease progression (decrease in 6MWD ≥15% on two separate days plus either worsening WHO functional class, need for new PAH-targeted medication, or decompensated right-sided heart failure). Clinical worsening was centrally adjudicated by independent PAH experts, masked to the randomisation.

Secondary efficacy endpoints at week 24 were tested hierarchically in the following order: change from baseline in 6MWD, NT-proBNP concentration, WHO functional class, and time to first clinical worsening event. Prespecified exploratory analyses included assessment of risk using three risk score calculators (REVEAL, COMPERA, and FPHN non-invasive scores). Components of the REVEAL risk score used in risk analysis are shown in the appendix (p 12).

Safety was assessed by recording adverse events and serious adverse events according to the Medical Dictionary for Regulatory Activities version 17.1 or higher, adverse events leading to discontinuation or death, and laboratory variables (appendix p 9).

Statistical analysis

Sample size was determined on the basis of previous study data from the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial (PATENT-1)[13] and RESPITE.[1,3,4] The rate of clinical improvement without clinical worsening at week 24 was estimated to be 40% for the riociguat group. Assuming a treatment effect of 50% for the riociguat group versus the PDE5i group, the estimate for achievement of the primary endpoint in the PDE5i group was 20%. A sample size of 218 patients was calculated using SAS software version 9.2 (with PROC POWER procedure, two-sample frequency, χ^2 test, two-sided alpha=5%, power=90%). With an estimated screening failure rate of 15%, 257 patients would need to be screened.

The primary endpoint was analysed using last observation carried forward (LOCF), with the riociguat and PDE5i groups compared using a stratified Mantel–Haenszel test with a two-sided alpha level of 5%. As LOCF was used, no adjustment for dropouts was needed (further information on how missing data were handled is provided in the appendix [p 10]). Treatment effects in prespecified

subgroups were calculated using the Cochran–Mantel–Haenszel method. Strata differences in these subgroups were assessed using logistic regression analyses where disease was stratum and model parameters were treatment and subgroup. Three predefined sensitivity analyses were done to assess the potential effect of missing values on the primary outcome (general estimating equations approach, multiple imputation with penalty, and tipping point analysis; appendix p 10). Secondary efficacy endpoints were tested hierarchically as described above. An alpha level of 5% was used for secondary and exploratory endpoints. Changes in 6MWD, NT-proBNP concentration, WHO functional class, and risk scores from baseline to week 24 were compared between riociguat and PDE5i groups using stratified Wilcoxon testing. Time to clinical worsening was analysed using Kaplan–Meier estimates. A post-hoc analysis was done on the basis of achievement of all three components of the composite primary endpoint, in the absence of clinical worsening.

The study was not overseen by a data monitoring committee. All variables were analysed descriptively with appropriate statistical methods (categorical variables by frequency tables and continuous variables by sample statistics) using SAS software version 9.2.

The primary analysis set was the full analysis set, defined as all randomised patients who received at least one dose of study medication and who had values at baseline and week 24 for the components of the composite primary endpoint at baseline. The safety analysis set comprised all patients who received at least one dose of study drug.

For full details of the statistical analysis see the appendix (p 10). REPLACE is registered with ClinicalTrials.gov, NCT02891850.

Role of the funding source

The funders of the study contributed to the study design and data interpretation, data collection, and writing of the report.

Results

Between Jan 11, 2017, and July 31, 2019, 293 patients were screened. 111 patients were randomly assigned to the riociguat group and 115 patients to the PDE5i group (figure 1). One patient assigned to the PDE5i group did not receive any dose of the study drug, so 225 patients were included in the safety analysis. One further patient in the PDE5i group had missing components of the composite endpoint at baseline and so was excluded from the primary efficacy analysis, resulting in a full analysis population of 224 patients. A total of 14 (6%) patients discontinued the study.

Baseline demographics and disease characteristics were generally similar between the treatment groups (table 1); however, the riociguat group had a slightly higher proportion of patients with PAH-CTD (24 [22%] *vs* 19 [17%]), patients aged 65 years and older (30 [27%] *vs* 22 [19%]), and male patients (29 [26%] *vs* 19 [17%]) than the PDE5i group. Median (IQR) NT-proBNP concentration was lower in the riociguat group than in the PDE5i group (table 1).

After the dose-adjustment period, 84 (78%) patients were receiving the maximum dose of riociguat (2·5 mg three times per day), nine (8%) patients were receiving 2·0 mg three times per day, and 15 (14%) patients were receiving lower doses (0·5, 1, or 1·5 mg). In the PDE5i group, the median daily dosage at week 8 was 60 mg (IQR 60–120) for sildenafil (n=77) and 40 mg (40–40) for tadalafil (n=33).

	Riociguat (n=111)	PDE5i (n=113)
Age, years	49·4 (16·2)	49·1 (15·7)
Age		
<65 years	81 (73%)	91 (81%)
≥65 years	30 (27%)	22 (19%)
Sex		
Male	29 (26%)	19 (17%)
Female	82 (74%)	94 (83%)
Ethnicity		
White	86 (77%)	88 (78%)
Black or African American	4 (4%)	5 (4%)
Asian	17 (15%)	19 (17%)
Other	1 (1%)	0
Not reported	3 (3%)	1 (1%)
Body-mass index, kg/m²	26·3 (5·0)	26·7 (5·2)
PAH classification		
Idiopathic PAH	69 (62%)	73 (65%)
Heritable PAH	4 (4%)	4 (4%)
Drug-induced and toxin-induced PAH	1 (1%)	4 (4%)
PAH-CTD	24 (22%)	19 (17%)
PoPH	7 (6%)	6 (5%)
PAH-CHD	6 (5%)	7 (6%)
Time from first diagnosis to randomisation, years	3 (1–7)	4 (1–10)
Monotherapy and combination therapy		
PDE5i monotherapy	32 (29%)	32 (28%)
PDE5i plus ERA combination therapy	79 (71%)	81 (72%)
PDE5i pretreatment		
Tadalafil	33 (30%)	33 (29%)
Sildenafil	78 (70%)	80 (71%)
ERA pretreatment		
Bosentan	19 (17%)	20 (18%)
Ambrisentan	30 (27%)	29 (26%)
Macitentan	30 (27%)	32 (28%)
6MWD, m	374 (60)	367 (62)
NT-proBNP concentration, pg/mL	290 (138–863)*	395 (166–1068)
WHO functional class 3	111 (100%)	113 (100%)

Data are mean (SD), n (%), or median (IQR). Data presented are from the full analysis set. 6MWD=6-min walk distance. ERA=endothelin receptor antagonist. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. PAH=pulmonary arterial hypertension. PAH-CHD=PAH associated with congenital heart disease. PAH-CTD=PAH associated with connective tissue disease. PDE5i=phosphodiesterase-5 inhibitor. PoPH=portopulmonary hypertension. *n=108.

Table 1: **Baseline patient demographics and disease characteristics**

After 24 weeks of treatment, the composite primary endpoint of clinical improvement in the absence of clinical worsening was achieved by 45 (41%) of 111 patients in the riociguat group and 23 (20%) of 113 patients in the PDE5i group (odds ratio [OR] 2·78 [95% CI 1·53–5·06]; p=0·0007; figure 2), with a relative risk of 1·99 (95% CI 1·30–3·06). The numbers of patients who achieved the individual components of the composite primary endpoint in the overall population and in the subgroup of patients who achieved the primary endpoint are shown in the appendix (p 13). All three sensitivity analyses demonstrated poor influence of missing values on the primary endpoint (appendix p 11). In addition, a numerical but non-significant difference between riociguat and PDE5i in favour of riociguat remained in the post-hoc analysis requiring achievement of all three components of the primary endpoint in the absence of clinical worsening (appendix p 11).

Through the course of the study, one (1%) patient in the riociguat group and 10 (9%) patients in the PDE5i group experienced a clinical worsening event (figure 2). Three patients died during the study, all in the PDE5i group. One additional patient in the PDE5i group died during the safety follow-up.

When treatment effect was assessed in predefined subgroups, no significant differences were found between strata for sex, baseline 6MWD, PAH subgroups, or combination therapy versus monotherapy (figure 3; appendix p 15). The significant differences found between strata in the age and baseline PDE5i pretreatment subgroups were not present upon multiple test correction (data not shown), indicating a high probability of a chance finding. Details of the achievement of the primary endpoint with different ERAs and PDE5i are shown in the appendix (pp 16–17). Assessment of sildenafil dosing

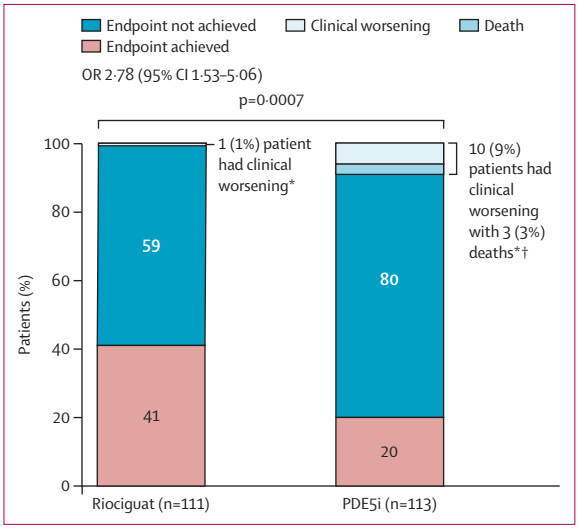

Figure 2: **Proportion of patients achieving the composite primary endpoint**
OR=odds ratio. PDE5i=phosphodiesterase-5 inhibitor. *Patients who experienced clinical worsening are a subgroup of those who did not achieve the primary endpoint. †Deaths are a subgroup of clinical worsening. An additional death occurred in the PDE5i group during the safety follow-up phase.

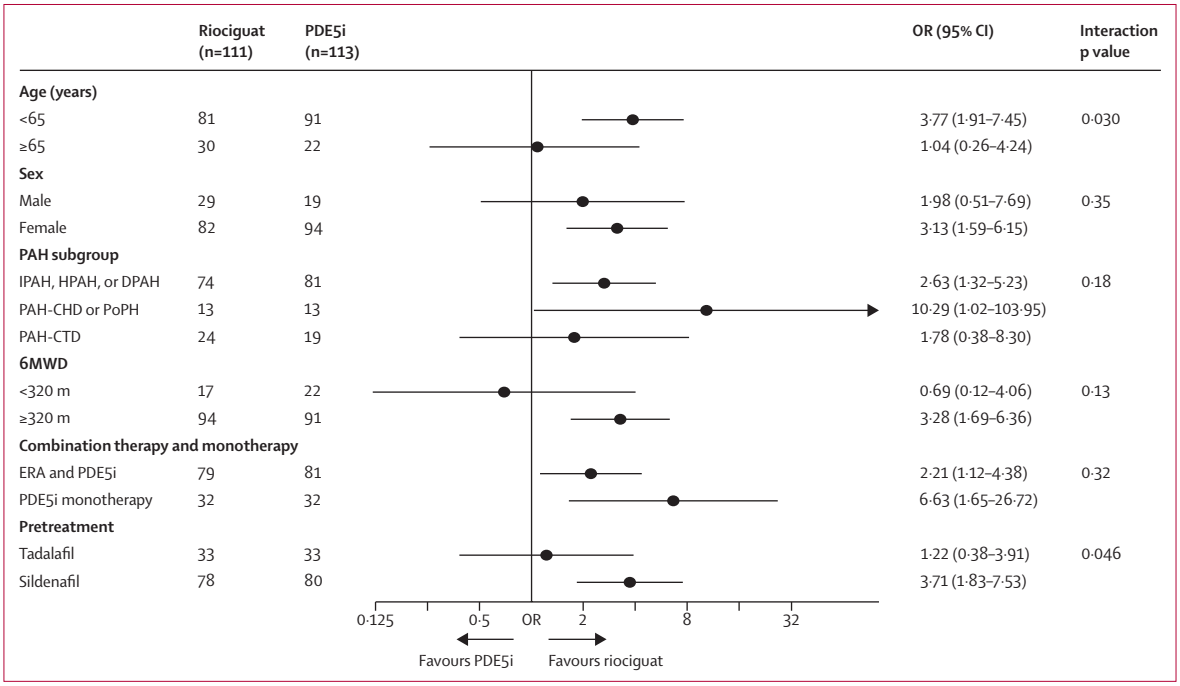

Figure 3: **Forest plot comparing patient achievement of the composite primary endpoint, by predefined subgroups**
6MWD=6-min walk distance. DPAH=drug-induced and toxin-induced PAH. ERA=endothelin receptor antagonist. HPAH=heritable PAH. IPAH=idiopathic PAH. OR=odds ratio. PAH=pulmonary arterial hypertension. PAH-CHD=PAH associated with congenital heart disease. PAH-CTD=PAH associated with connective tissue disease. PDE5i=phosphodiesterase-5 inhibitor. PoPH=portopulmonary hypertension.

at baseline in the riociguat group showed no relationship between baseline dose and achievement of the primary endpoint (appendix p 18).

In the hierarchical analysis of secondary endpoints, riociguat improved mean 6MWD over time, from 374 m (SD 60) at baseline to 410 m (95) at week 24 (mean change 36 [66]). Mean 6MWD improved to a lesser extent with PDE5i, from 367 m (62) at baseline to 381 m (89) at week 24 (mean change 14 [67]; mean treatment difference 23 m [95% CI 5–40]; p=0·054; figure 4A). The median values for change in 6MWD were 30 m (IQR –6 to 61) in the riociguat group and 14 m (–14 to 50) in the PDE5i group. For NT-proBNP, the mean change from baseline to week 24 was –88 pg/mL (534) in the riociguat group and 81 pg/mL (1268) in the PDE5i group (mean treatment difference –170 pg/mL [–426 to 87]; p=0·11; figure 4B). Riociguat treatment resulted in improvements in WHO functional class from baseline to week 24, with three (3%) patients with functional class 1, 46 (41%) with functional class 2, 60 (54%) with functional class 3, two (2%) with functional class 4, and no patients with functional class 5 at week 24, compared with three (3%), 23 (20%), 81 (72%), four (4%), and two (2%) of patients in the PDE5i group, respectively (WHO functional class 5 represents patients who died before the study ended). At week 24, a higher proportion of patients in the riociguat group had improved WHO functional class than in the PDE5i group (mean difference –0·26 [–0·42 to –0·11]; p=0·0007; figure 4C).

During the 24-week treatment period, PAH treatment was escalated in two (2%) patients in the riociguat group and in nine (8%) patients in the PDE5i group. As per the study protocol, treatment escalations in four patients were not adjudicated as clinical worsening; of these, one patient in the riociguat group received subcutaneous treprostinil and three patients in the PDE5i group received selexipag. Treatment escalations in the remaining seven patients were adjudicated as clinical worsening: one patient in the riociguat group started subcutaneous treprostinil, and in the PDE5i group, two patients started selexipag, one received subcutaneous treprostinil, one started bosentan, and two started inhaled iloprost. Two (2%) additional patients in the

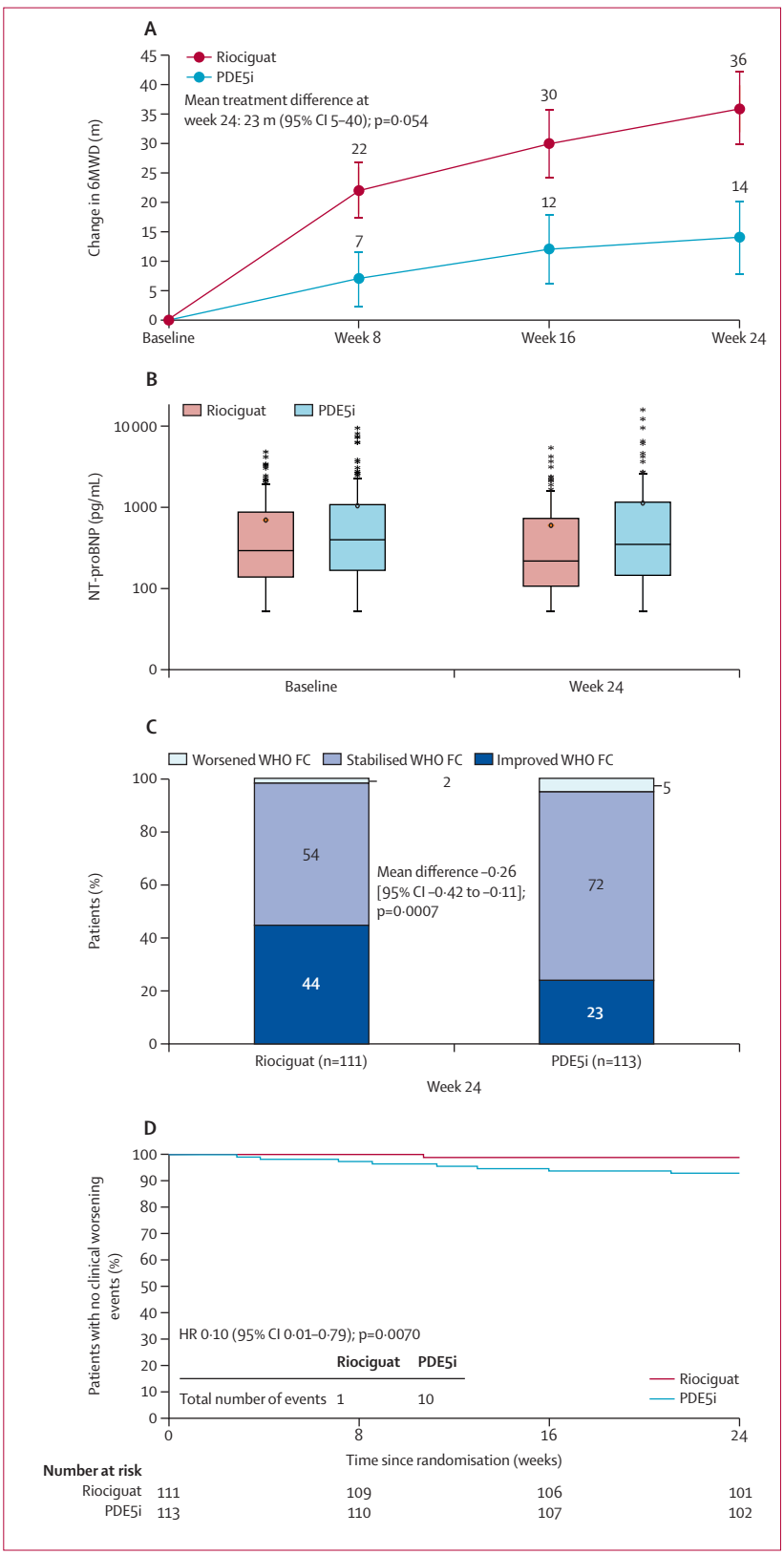

Figure 4: **Changes in secondary outcomes from baseline to week 24**
(A) Graph shows mean change in 6MWD. Error bars are SEM. (B) Boxplot shows change in NT-proBNP concentration. The bottom and top of the boxes are the first and third quartiles. The open circles indicate mean values. The lines inside the boxes indicate the median values. The whiskers that extend from each box indicate the range of values outside of the IQR, but are within a distance less than or equal to 1·5 × IQR. Individual observations beyond the whiskers are denoted with an *. (C) Graph shows proportion of patients with improved, stable, or worsened WHO FC. (D) Graph shows proportion of patients who did not experience clinical worsening over 24 weeks. Patients were censored at end of study if they did not experience clinical worsening. Overall, 110 patients in the riociguat group and 103 patients in the PDE5i group were censored. 6MWD=6-min walk distance. FC=functional class. HR=hazard ratio. NT-proBNP= *N*-terminal prohormone of brain natriuretic peptide. PDE5i=phosphodiesterase-5 inhibitor.

	Riociguat (n=111)	PDE5i (n=114)
Any adverse event during first 48 h (PDE5i washout period for riociguat group)	2 (2%)	12 (11%)
Any adverse event	79 (71%)	75 (66%)
Occurring during 8-week dose-adjustment period	61 (55%)	51 (45%)
Occurring after 8-week dose-adjustment period	55 (50%)	56 (49%)
Adverse events reported in >5% of patients in either treatment group		
Hypotension*	15 (14%)	6 (5%)
Headache	14 (13%)	8 (7%)
Dyspepsia	10 (9%)	0
Gastroesophageal reflux disease	8 (7%)	1 (1%)
Nasopharyngitis	8 (7%)	5 (4%)
Diarrhoea	6 (5%)	3 (3%)
Fatigue	6 (5%)	2 (2%)
Chest pain	5 (5%)	6 (5%)
Upper respiratory tract infection	4 (4%)	7 (6%)
Dyspnoea	3 (3%)	6 (5%)
Sinusitis	2 (2%)	6 (5%)
Back pain	1 (1%)	6 (5%)
Cough	0	7 (6%)
Any severe adverse event	10 (9%)	12 (11%)
Any serious adverse event	8 (7%)	19 (17%)
Serious adverse events reported in more than one patient in either treatment group		
Pneumonia	0	2 (2%)
Pulmonary arterial hypertension†	0	2 (2%)
Pulmonary hypertension†	0	2 (2%)
Hypotension	2 (2%)	0
Adverse events leading to death	0	3 (3%)‡
Adverse events leading to study drug discontinuation	6 (5%)	1 (1%)
Adverse events of special interest	6 (5%)	2 (2%)
Symptomatic hypotension	6 (5%)	2 (2%)
Haemoptysis or pulmonary haemorrhage	0	0

Data are n (%). PDE5i=phosphodiesterase-5 inhibitor. *Includes symptomatic and asymptomatic hypotension. †Preferred term for worsening of the condition. ‡An additional death occurred in the safety follow-up period.

Table 2: **Summary of adverse events and most frequently reported adverse events**

PDE5i group had been taking selexipag and beraprost before study treatment (protocol violations).

At week 24, clinical worsening events occurred in one (1%) of 111 patients in the riociguat group (hospitalisation due to worsening PAH) and 10 (9%) of 114 patients in the PDE5i group (hospitalisation due to worsening PAH [n=9]; disease progression [n=1]; OR 0·10 [0·01–0·73]; p=0·0047; figure 2; appendix p 14). This result was consistent across PAH subgroups, with a higher proportion of patients experiencing adjudicated clinical worsening events with PDE5i versus riociguat in all subgroups (appendix p 14). Time to the first adjudicated clinical worsening event was longer with riociguat compared with PDE5i (hazard ratio 0·10 [95% CI 0·01–0·79]; p=0·0070; figure 4D).

In the safety analysis, adverse events overall were reported in similar proportions of patients in the riociguat group (79 [71%] patients) and the PDE5i group (75 [66%] patients; table 2). During the first 48 h (PDE5i washout period in the riociguat group), the incidence of adverse events was lower in the riociguat group (two [2%] patients) than in the PDE5i group (12 [11%] patients; table 2). Overall, the most frequently occurring adverse events were hypotension (15 [14%]), headache (14 [13%]), and dyspepsia (10 [9%]) in the riociguat group and headache (eight [7%]), cough (seven [6%]), and upper respiratory tract infection (seven [6%]) in the PDE5i group (table 2). Adverse events considered to be related to the study drug occurred in 44 (40%) patients in the riociguat group and in four (4%) patients in the PDE5i group. More patients experienced serious adverse events in the PDE5i group (19 [17%]) than in the riociguat group (eight [7%]; table 2), with serious adverse events considered to be related to the study drug occurring in two (2%) patients in the riociguat group and in no patients in the PDE5i group. Adverse events of special interest were reported in six (5%) patients in the riociguat group and two (2%) patients in the PDE5i group, all of which were symptomatic hypotension. No cases of haemoptysis occurred in either group (table 2).

Adverse events leading to discontinuation of study drug were more frequent in the riociguat group (six [5%]) than in the PDE5i group (one [1%]). In the riociguat group, six patients discontinued study treatment due to events of right ventricular failure, upper abdominal pain, diarrhoea, fatigue, dizziness, headache, dyspnoea, and hypotension (each occurring in one [1%] patient), and exertional dyspnoea (two [2%] patients). Patients could experience more than one adverse event leading to discontinuation. In the PDE5i group, one (1%) patient discontinued due to an adverse event of drug therapy enhancement. Three (3%) patients in the PDE5i group experienced an adverse event with an outcome of death (appendix p 11). An additional patient (1%) in the PDE5i group died during the safety follow-up due to worsening of pulmonary hypertension. No patients in the riociguat group died.

In the prospective exploratory analysis assessing changes in risk scores, a higher proportion of patients in the riociguat group versus the PDE5i group improved to a low-risk stratum at week 24 with all three PAH risk score calculators (appendix p 19). Numerically greater improvements in the mean change for REVEAL score were observed for riociguat compared with PDE5i (–0·68 [SD 1·61] versus –0·51 [1·70]), although this difference was not significant (mean difference –0·16 [95% CI –0·60 to 0·27]; p=0·31). Significant improvements in the riociguat group versus the PDE5i group were seen in the COMPERA score (mean change from baseline to week 24 –0·36 [0·52] *vs* –0·25 [0·45]; mean difference –0·11 [–0·24 to 0·02]; p=0·050) and the FPHN non-invasive score (0·78 [1·03] *vs* 0·50 [0·92]; mean difference 0·28 [0·02–0·54]; p=0·017).

Discussion

The REPLACE trial assessed the efficacy of switching to riociguat from PDE5i versus continuing PDE5i (with or without an ERA) in patients with PAH at intermediate risk of 1-year mortality (based on ESC–ERS guideline thresholds for 6MWD and WHO functional class).[2,3] To our knowledge, this is the only randomised trial to directly compare any two active PAH therapies. The composite primary endpoint was met, with significantly more patients achieving clinical improvement in the absence of clinical worsening at 24 weeks after switching to riociguat compared with continuing PDE5i. Switching also reduced the incidence of adjudicated clinical worsening events (death, hospitalisation for worsening PAH, or disease progression) compared with continuing PDE5i. This was driven primarily by a lower rate of hospitalisation with riociguat, and PAH-related morbidity and hospitalisation are known to be important prognostic factors in subsequent PAH mortality.[18] Overall, these results reinforce data from RESPITE, which suggested that switching to riociguat from a PDE5i was beneficial and well tolerated in patients who had not reached their treatment goal with PDE5i.[15]

Given the recent emphasis on the importance of risk reduction,[6,7,17,19,20] REPLACE used a novel primary endpoint focused on measuring improvements in components of standardised risk assessments—6MWD, WHO functional class, and NT-proBNP concentration. The primary endpoint result favouring riociguat was consistent, as shown by a high level of internal concordance across the prespecified subgroups and secondary endpoints, and was supported by findings for the adjudicated clinical worsening.

In the analyses of secondary endpoints, switching to riociguat led to significant improvements in WHO functional class from baseline to week 24 compared with PDE5i maintenance therapy. The 36-m improvement from baseline in 6MWD observed with riociguat is similar to that reported in PATENT-1 (30 m in the riociguat 2·5 mg group),[13] an impressive result given that all patients in REPLACE had been receiving treatments proven to be effective in randomised, placebo-controlled studies before switching to riociguat whereas in PATENT, 50% of the patients were treatment-naive. The improvements from baseline with riociguat in WHO functional class and 6MWD in REPLACE are also consistent with findings from RESPITE.[15] Changes in NT-proBNP concentration in REPLACE, however, were less pronounced than in RESPITE. It should be noted that in REPLACE, baseline NT-proBNP concentration was lower with riociguat than PDE5i, and less than half the baseline value in RESPITE. Although there is no obvious explanation for this difference, there was still improvement with riociguat, despite the lower baseline value in this group. Overall, the changes in NT-proBNP concentration, which was chosen as an objective parameter, were moderate and smaller than expected, with improvements in NT-proBNP concentration not possible in some patients as their baseline reading was below the lower limit of measurement. There were also individual outliers, which is consistent with data from both PATENT-1 and RESPITE, which also reported wide variability in NT-proBNP concentrations.[13,15] Therefore, questions remain over the use of NT-proBNP as a component of composite endpoints or as an individual endpoint in future studies.

Furthermore, exploratory analysis of three validated risk assessment scores—REVEAL, COMPERA, and the FPHN non-invasive risk scores—showed that switching to riociguat improved patient risk status compared with PDE5i maintenance, further supporting the primary efficacy analysis results. More than half of patients were evaluated as low risk at baseline using the REVEAL risk score, despite all patients being in WHO functional class 3. This finding is consistent with analyses of REVEAL scores in PATENT-1, and also of patients with chronic thromboembolic pulmonary hypertension in Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1), in which most patients (233 [59%] in PATENT-1; 130 [55%] in CHEST-1) were assessed as low risk by REVEAL, despite a high proportion (212 [54%] in PATENT-1; 154 [65%] in CHEST-1) of patients being in WHO functional class 3.[21,22] This might also explain the smaller proportion of patients improving to low risk with the REVEAL risk score than with the COMPERA and FPHN non-invasive risk scores in REPLACE.

The REPLACE protocol allowed patients in either group to receive treatment escalation at any time during the study if deemed necessary by the investigator. Although more patients in the PDE5i group had treatment escalation than in the riociguat group, some of which took place in the absence of protocol-defined, centrally adjudicated clinical worsening, the overall number of treatment escalations was low. In the patients on PDE5i, who knew they were continuing their previous therapy, a higher frequency of treatment escalation might have been expected. It is possible that inclusion in a clinical study of a defined duration, with close monitoring, might explain this observation.

No safety signal was observed when switching from a PDE5i to riociguat, as demonstrated by similar adverse event rates between treatment groups, no increased incidence of adverse events during PDE5i washout, and a higher incidence of serious adverse events with PDE5i. The higher number of drug-related adverse events in the riociguat group might reflect the bias of unblinded safety assessments by the investigators. The safety results from patients switching to riociguat were consistent with the known safety profile of riociguat.[13,23,24]

Several possible underlying mechanisms might be considered to explain the findings from REPLACE. First, the improvements observed when switching to riociguat

might be due to the different modes of action of riociguat and PDE5i within the NO–sGC–cGMP pathway. While low NO and cGMP levels from a defective NO–sGC–cGMP pathway in patients with PAH might limit PDE5i efficacy, riociguat functions independently of NO, upstream of cGMP, and could, therefore, be more effective than PDE5 inhibition. A habituation effect for treatment with riociguat might also be possible—clinical practice often shows that the effects of drug treatment can wear off with time, although patient non-compliance might be associated with this observation. Additionally, patients taking sildenafil at baseline and switching to riociguat had a tendency to meet the primary endpoint more frequently than those switching from tadalafil (figure 3; appendix p 17), with patients more likely to experience clinical worsening or death when remaining on tadalafil than sildenafil. Although the labelled dose for sildenafil in PAH is 60 mg daily maximum, higher doses were studied in the registration trial and the long-term extension study,[11,25] and it is possible that higher doses might be beneficial for some patients. However, in REPLACE, patients taking a higher dose of sildenafil at baseline were just as likely to improve when switching to riociguat as those taking 60 mg per day (appendix p 18).

Strengths of the study include the independent, blinded central adjudication of the primary endpoint by the Clinical Endpoint Committee, including the components of clinical worsening. 6MWD and WHO functional class, which were components of the primary endpoint as well as individual secondary endpoints, were assessed by investigators masked to treatment allocation. Furthermore, treatment escalation was permitted at the discretion of the treating investigator, so patients were not left to deteriorate or obliged to withdraw from the study. Consistent treatment effects were seen across most predefined subgroups, including in patients stratified by PAH subtype, despite those with PAH-CTD historically not responding as well to treatment as those with PAH of other causes. The significant differences found between patients aged 65 years or older and younger than 65 years, and between patients receiving sildenafil and tadalafil at baseline for pretreatment were not present upon multiple test correction, indicating a high probability of chance findings.

The central limitation is the open-label nature of the study, which was debated among the steering committee and sponsor when the study was designed. Ultimately, the problems of conducting a double-blind, double-dummy study that included both sildenafil and tadalafil proved insurmountable. Therefore, the protocol attempted to mitigate this by requiring sites to have separate investigators assigned to assess WHO functional class and 6MWD, who had no involvement in adverse event assessment or study drug administration, while trial monitors attempted to assess compliance with this protocol requirement. Nonetheless, participants knew their study treatment assignment, and this knowledge could have influenced their symptom reporting and their motivation, with potential impact on WHO functional class and 6MWD. REPLACE does not provide data on long-term outcomes, although 24 weeks allowed us to measure a difference in time to clinical worsening. In recent event-driven trials, the treatment effects between different groups, have been evident at or by 24 weeks, suggesting that this timeframe is probably sufficient to measure important differences in clinical outcomes.[26–29] Some baseline demographics and disease characteristics that are predictive of worse outcome[30]—ie, patients aged 65 years and older, male patients, and patients with PAH-CTD—were more common in the riociguat group than in the PDE5i group. Baseline NT-proBNP concentrations were lower in the riociguat group than in the PDE5i group, making it more difficult for patients in the riociguat group to achieve significant reductions in NT-proBNP concentration after 24 weeks. All these differences favour the PDE5i group and might have contributed to the relatively high response rate in patients who maintained PDE5i therapy. The addition of targeted PAH drugs during the study could also have potentially biased the results in favour of PDE5i maintenance. Further, there was no geographical stratification of the results by country or study centre, so cluster correlations could not be excluded, although given the large number of hospitals relative to the total number of patients, correlation would be unlikely. Finally, it is important to note that the results of REPLACE apply only to patients with intermediate-risk PAH and should not be extrapolated to other subgroups, especially those with high-risk PAH. Future areas of research could include the role of early riociguat therapy in patients with less severe PAH to maintain their low-risk profile.

In summary, findings from the REPLACE study demonstrated that patients on a stable dose of PDE5i treatment at intermediate risk of 1-year mortality can benefit from switching to riociguat. Switching from PDE5i therapy to riociguat, a drug that also acts via the NO–sGC–cGMP pathway, might therefore be a viable treatment escalation option for these patients.

Contributors

MMH, HAG, GS, CM, and MC designed the study. MMH, HAG, RLB, PAC, JSRG, JRK, DL, VVM, AJP, SR, AV-N, RJW, and GS acted as an advisory committee for the study. MMH, HAG, HA-H, RLB, S-AC, PAC, JSRG, EG, PJ, JRK, DL, VVM, GMBM, JO-A, AJP, TP, SR, CDV, AV-N, RJW, and GS collected and interpreted the data. MMH, CM, and KP accessed and verified the data. FK undertook statistical analyses. MMH wrote the abstract, introduction, and substantial parts of the remaining manuscript. All authors critically reviewed and revised the manuscript and approved the final version for publication. All authors had full access to study data and had final responsibility for the decision to submit for publication.

Declaration of interests

MMH has received fees for consultations and lectures from Acceleron, Actelion, Bayer, Janssen, Merck Sharpe & Dohme (MSD), and Pfizer. HA-H is an investigator of clinical studies with Actelion, Bayer AG, and Pfizer. RLB reports grants from Bellerophon, Bayer AG, Actelion, and EIGER. PAC reports grants and personal fees from Bayer AG, Actelion, and GlaxoSmithKline (GSK). JSRG reports grants and personal fees

from Actelion, Bayer AG, United Therapeutics, and MSD, personal fees from Arena, Bellopheron, Acceleron, Complexa, and Pfizer, and grants from GSK and Amco. EG reports fees for lectures and consultations from Actelion, Bayer AG, GSK, MSD, United Therapeutics, and Pfizer. PJ reports personal fees from Actelion, Bayer AG, Reata Pharmaceuticals, AOP Orphan, and MSD, and is an investigator for Actelion, Bayer AG, and Reata Pharmaceuticals. JRK reports that his institution has received grant support for clinical trials and basic science research in pulmonary hypertension from Actelion, Bayer, Lung Biotechnology, and United Therapeutics. DL reports honoraria, consultation fees, research support, and travel expenses from Actelion, Arena, Bayer AG, Northern Therapeutics, PhaseBio, and United Therapeutics. VVM has received research support or grants from Acceleron Pharma, Actelion, Bayer AG, Reata Pharmaceuticals, SoniVie, and United Therapeutics, and has served as a consultant and on advisory committees for Acceleron, Actelion, Altavant, Bayer, Caremark, CiVi BioPharma, Gossamer, Liquidia, and United Therapeutics. GMBM reports lecture and consultation fees from Bayer AG, Eli Lilly, and GSK. ASP reports fees for research grants, support for travel to meetings, and honoraria from Actelion, Bayer AG, GSK, MSD, Pfizer, and United Therapeutics. TP reports grants and personal fees from Actelion–Janssen, grants from United Therapeutics, Reata Pharmaceuticals, and Bayer, and personal fees from Bayer and Pfizer. SR reports remunerations for lectures and consultancy from Abbott, Acceleron, Actelion, Arena, Bayer, Bristol-Myers Squibb, Ferrer, GSK, Janssen, MSD, Novartis, Pfizer, and United Therapeutics, and research support to his institution from Actelion, Bayer, Novartis, Pfizer, and United Therapeutics. AV-N is supported by the Netherlands CardioVascular Research Initiative (CVON-2012-08 PHAEDRA, CVON-2017-10 DOLPHIN-GENESIS) and the Netherlands Organization for Scientific Research (NWO-VICI: 918.16.610, funding outside of the current study), has received speakers fees from Johnson & Johnson and Ferrer in the past 3 years, and served as a member of the scientific advisory board of Morphogen-XI. RJW reports grants and personal fees from Bayer AG and personal fees from MSD. MC, FK, CM, and KP are employees of Bayer AG. HAG reports personal fees and consultancy fees from Actelion, Bayer AG, GSK, Novartis, and Pfizer, consultancy fees from Bellerophon Pulse Technologies and MSD, and grants from Deutsche Forschungsgemeinschaft. GS reports personal fees and non-financial support from Actelion, Bayer, and MSD. S-AC, CDV, and JO-A declare no competing interests.

Data sharing

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing, pertaining to scope, timepoint, and process of data access. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union as necessary for doing legitimate research. This commitment applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after Jan 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to do further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Acknowledgments

Bayer AG and Merck Sharpe & Dohme co-funded the REPLACE study and both provided critical review of the manuscript. Medical writing assistance was provided by Robyn Bradbury (Adelphi Communications Ltd, Bollington, UK), funded by Bayer AG (Berlin, Germany) in accordance with Good Publications Practice 3. The authors would like to thank the investigators, patients, and the independent adjudication committee for their involvement in the study.

References

1 Humbert M, Lau EM, Montani D, Jais X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation* 2014; **130:** 2189–208.

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 Heart J* 2016; **37:** 67–119.

3 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:** 903–75.

4 Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019; **53:** 1801889.

5 Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018; **39:** 4175–81.

6 Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; **50:** 1700889.

7 Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017; **50:** 1700740.

8 Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N Engl J Med* 2009; **361:** 1864–71.

9 Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995; **333:** 214–21.

10 Tsai EJ, Kass DA. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. *Pharmacol Ther* 2009; **122:** 216–38.

11 Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 2148–57.

12 Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119:** 2894–903.

13 Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; **369:** 330–40.

14 Hoeper MM, Klinger JR, Benza RL, et al. Rationale and study design of RESPITE: an open-label, phase 3b study of riociguat in patients with pulmonary arterial hypertension who demonstrate an insufficient response to treatment with phosphodiesterase-5 inhibitors. *Respir Med* 2017; **122:** S18–22.

15 Hoeper MM, Simonneau G, Corris PA, et al. RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors. *Eur Respir J* 2017; **50:** 1602425.

16 Hoeper MM, Ghofrani HA, Benza RL, et al. Rationale and design of the REPLACE trial: Riociguat rEplacing Phosphodiesterase 5 Inhibitor (PDE5i) therapy evaLuated against Continued PDE5i thErapy in patients with pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med* 2017; **195:** A2296.

17 Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. *J Heart Lung Transplant* 2015; **34:** 356–61.

18 McLaughlin VV, Hoeper MM, Channick RN, et al. Pulmonary arterial hypertension-related morbidity is prognostic for mortality. *J Am Coll Cardiol* 2018; **71:** 752–63.

19 Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from REVEAL. *Chest* 2012; **142:** 448–56.

20 Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; **122:** 164–72.

21 Benza RL, Farber HW, Frost A, et al. REVEAL risk scores applied to riociguat-treated patients in PATENT-2: Impact of changes in risk score on survival. *J Heart Lung Transplant* 2018; **37:** 513–9.

22 Benza RL, Farber HW, Frost A, et al. REVEAL risk score in patients with chronic thromboembolic pulmonary hypertension receiving riociguat. *J Heart Lung Transplant* 2018; **37:** 836–43.

23 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:** 1303–13.

24 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:** 361–71.

25 Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: SUPER-2. *Chest* 2011; **140:** 1274–83.

26 Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015; **373:** 2522–33.

27 Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; **369:** 809–18.

28 Galiè N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; **373:** 834–44.

29 White RJ, Jerjes-Sanchez C, Bohns Meyer GM, et al. Combination therapy with oral treprostinil for pulmonary arterial hypertension. A double-blind placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2020; **201:** 707–17.

30 Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL registry. *Chest* 2015; **148:** 1043–54.