Switching from phosphodiesterase type 5 inhibitors to riociguat in patients with pulmonary arterial hypertension: The REPLACE study

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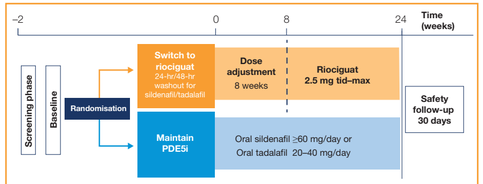
Background

- Pulmonary arterial hypertension (PAH) treatment guidelines recommend patients achieve or maintain a low-risk profile[1–3] but many receiving PAH-targeted therapy do not meet this goal.[4–6]
- Riociguat and phosphodiesterase type 5 inhibitors (PDE5i), both therapies approved for treatment of PAH, act on the same pathway via different mechanisms.[7]
- REPLACE aimed to assess the effect of switching to riociguat versus PDE5i maintenance in patients with PAH at intermediate risk.

Methods

- REPLACE (NCT02891850) was a randomised, open-label, 24-week, multicentre Phase 4 study.
- Patients with PAH at intermediate risk, defined as World Health Organization functional class (WHO FC) III with a 6-minute walking distance (6MWD) of 165–440 m, despite receiving stable doses of PDE5i ± an endothelin receptor antagonist (ERA), were included.
- Patients were randomised to remain on PDE5i or switch to riociguat (2.5 mg three times daily [tid]–maximum) (Figure 1); ERA pretreatment continued in both groups.



PDE5i, phosphodiesterase type 5 inhibitors; tid, three times daily.

Figure 1. REPLACE study design

- The blinded, centrally adjudicated composite primary endpoint was clinical improvement at Week 24 (defined as two of the following: ≥10%/≥30 m increase in 6MWD from baseline, WHO FC I/II, or ≥30% reduction in *N*-terminal prohormone of brain natriuretic peptide [NT-proBNP] from baseline) in the absence of clinical worsening (death from any cause, hospitalisation for worsening PAH, or disease progression).
- Secondary endpoints included change from baseline at Week 24 in 6MWD, NT-proBNP, WHO FC and time to first clinical worsening.
  - 6MWD and WHO FC were assessed blind and clinical worsening events were independently adjudicated.
- Adverse events (AEs) were assessed throughout the study and the 30-day safety follow-up.

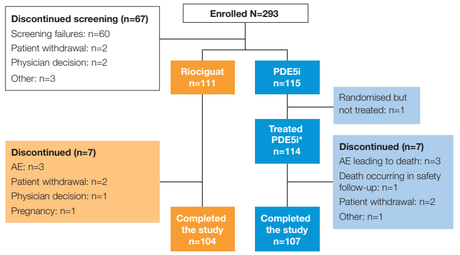
Results

Patients

- Overall, 111 patients were randomised to riociguat and 115 patients to PDE5i (Figure 2).
- Baseline demographics and disease characteristics were generally similar between the treatment groups (Table 1).

Treatment received

- After dose adjustment, 84 patients (78%) reached the maximum dose of riociguat 2.5 mg tid, nine patients (8%) were receiving 2.0 mg tid, and 15 patients (14%) were receiving lower doses.



Includes the 24-week treatment period and 30-day safety follow-up.
*One patient was missing components of the primary endpoint at baseline (safety analysis set=114, full analysis set=113).
AE, adverse event; PDE5i, phosphodiesterase type 5 inhibitor.

Figure 2. Patient disposition

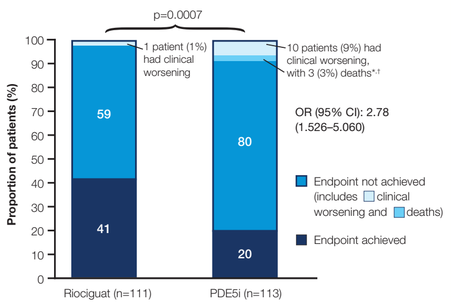
Table 1. Baseline demographics and disease characteristics

	Riociguat (n=111)	PDE5i (n=113)	Total (n=224)
Age (years)	49 (16)	49 (16)	49 (16)
<65 years/≥65 years	81 (73) / 30 (27)	91 (81) / 22 (19)	172 (77) / 52 (23)
Female	82 (74)	94 (83)	176 (79)
Body mass index (kg/m²)	26.3 (5.0)	26.7 (5.2)	26.5 (5.1)
PAH classification			
Idiopathic PAH	69 (62)	73 (65)	142 (63)
Heritable PAH	4 (4)	4 (4)	8 (4)
Drug- and toxin-induced PAH	1 (1)	4 (4)	5 (2)
PAH-CTD	24 (22)	19 (17)	43 (19)
PoPH	7 (6)	6 (5)	13 (6)
PAH-CHD	6 (5)	7 (6)	13 (6)
Time from first diagnosis to randomisation (years)	6 (8)	6 (7)	6 (7)
PDE5i monotherapy	32 (29)	32 (28)	64 (29)
PDE5i plus ERA combination therapy	79 (71)	81 (72)	160 (71)
6MWD (m)	374 (60)	367 (62)	370 (61)
NT-proBNP (pg/mL), median (range)	290 (51–4771)*	395 (51–9365)	352 (51–9365)†
WHO FC III	111 (100)	113 (100)	224 (100)

Data are mean (SD) or n (%), unless otherwise stated.
*n=108. †n=221.
6MWD, 6-minute walking 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 type 5 inhibitor; PoPH, portopulmonary hypertension; SD, standard deviation; WHO FC, World Health Organization functional class.

Composite primary endpoint

- Clinical improvement in the absence of clinical worsening was achieved by 45 patients (41%) with riociguat and 23 patients (20%) with PDE5i; odds ratio (OR) 2.78 (95% confidence interval [95% CI]: 1.53–5.06); p=0.0007 (Figure 3).



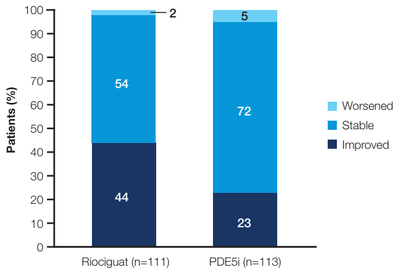
OR, 95% CI, and p-value calculated by a stratified Mantel–Haenszel test stratified by PAH class at baseline. *Patients who experienced clinical worsening are a subgroup of those who did not achieve the endpoint. †Deaths are a subgroup of clinical worsening. An additional death occurred in the PDE5i group during the safety follow-up phase.
CI, confidence interval; OR, odds ratio; PDE5i, phosphodiesterase type 5 inhibitor.

Figure 3. Proportion of patients achieving the composite primary endpoint

- Clinical improvement in the absence of clinical worsening was achieved regardless of type of PDE5i monotherapy or PDE5i/ERA combination therapy, or sildenafil dose at baseline, and was generally consistent across all other predefined subgroups.

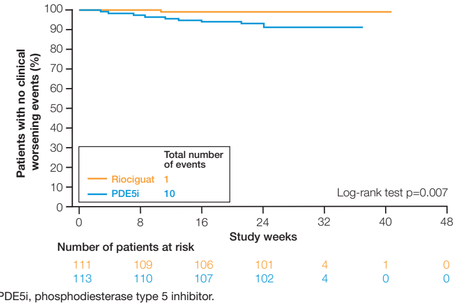
Secondary endpoints

- From baseline to Week 24, numerically greater improvements in 6MWD (mean treatment difference [95% CI]: 23 m [5–40 m]; p=0.0542) and NT-proBNP (mean treatment difference [95% CI]: –170 pg/mL [–426 to 87]; p=0.1067) were observed with riociguat versus PDE5i.
- Significant improvements in WHO FC were observed with riociguat versus PDE5i (mean difference [95% CI]: –0.26 [–0.42 to –0.11]; p=0.0007) (Figure 4).



P-value for Wilcoxon test for mean difference versus PDE5i. FC, functional class; PDE5i, phosphodiesterase type 5 inhibitor; WHO, World Health Organization.

Figure 4. Proportion of patients with worsened, stable, and improved WHO FC at Week 24



PDE5i, phosphodiesterase type 5 inhibitor.

Figure 5. Kaplan–Meier analysis of time to clinical worsening

Table 2. Safety summary

Event, n (%)	Riociguat (n=111)	PDE5i (n=114)
AEs during first 48 hours (PDE5i washout period for riociguat group)	2 (2)	12 (11)
Any AE	79 (71)	75 (66)
AE occurring during 8-week dose-adjustment period	61 (55)	51 (45)
AE occurring after 8-week dose-adjustment period	55 (50)	56 (49)
AEs reported in ≥5% of patients in either treatment group		
Hypotension*	15 (14)	6 (5)
Headache	14 (13)	8 (7)
Dyspepsia	10 (9)	0
Gastro-oesophageal 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 AE	10 (9)	12 (11)
Any SAE	8 (7)	19 (17)
SAEs reported in >1 patient in either treatment group		
Pneumonia	0	2 (2)
Pulmonary arterial hypertension†	0	2 (2)
Pulmonary hypertension†	0	2 (2)
Hypotension	2 (2)	0
AEs leading to death	0	3 (3)‡
AEs leading to study drug discontinuation	6 (5)	1 (1)
AEs of special interest	6 (5)	2 (2)
Symptomatic hypotension	6 (5)	2 (2)
Haemoptysis/pulmonary haemorrhage	0	0

*Includes symptomatic and asymptomatic hypotension. †Preferred term for worsening of the condition. ‡An additional death occurred in the safety follow-up period.
AE, adverse event; PDE5i, phosphodiesterase type 5 inhibitor; SAE, serious adverse event.

- At Week 24, significantly fewer riociguat patients (1%; n=1) versus PDE5i patients (9%; n=10) experienced an adjudicated clinical worsening event (OR 0.10 [95% CI: 0.013–0.725]; p=0.0047); this observation was consistent across all PAH subgroups (data not shown).
  - Time to the first adjudicated clinical worsening event was significantly longer with riociguat versus PDE5i (p=0.007) (Figure 5).

Safety

- The frequency of AEs was similar between treatment groups but more patients reported serious AEs with PDE5i versus riociguat (Table 2).
- No new safety signals were observed when switching from PDE5i to riociguat.

Conclusions

- **Patients switching from PDE5i to riociguat had a significantly higher likelihood of clinical improvement and significantly reduced rate of clinical worsening compared with patients remaining on PDE5i.**
- **Riociguat was well tolerated in patients switching from PDE5i, and safety data were consistent with the known profile of the drug.**
- **Switching from PDE5i to riociguat can benefit patients with PAH at intermediate risk and could serve as a strategic option for treatment escalation.**

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