Purpose
The REPLACE study (NCT02891850) will investigate the potential efficacy and safety benefits of switching to riociguat versus continued treatment with PDE5i therapy in patients with pulmonary arterial hypertension (PAH).

Background
A significant proportion of patients with PAH fail to achieve or maintain treatment goals with PDE5i therapy. This may indicate impairment of the nitric oxide–soluble guanylate cyclase (sGC) pathway, leading to insufficient endogenous cyclic guanosine monophosphate levels. Data from the single-arm, open-label RESPITE study provided preliminary evidence that these patients may benefit from switching from PDE5i to riociguat, an sGC stimulator.

Methods
REPLACE is a prospective, randomized, international, multicenter, two-arm, 24-week, controlled, open-label study in patients aged 18–75 years with PAH who do not achieve or maintain treatment goals with PDE5i therapy. Insufficient clinical response to PDE5i therapy at screening is determined by: World Health Organization (WHO) functional class (FC) III and 6-minute walking distance (6MWD) 165–440 m, despite stable doses of PDE5i with or without background endothelin receptor antagonists (ERAs). Eligible patients will be randomized to remain on PDE5i treatment (sildenafil 60 mg minimum daily or once-daily tadalafil 20–40 mg) or switch to riociguat up to a maximum of 2.5 mg tid (dose adjusted from a starting dose of 1.0 mg tid) (figure). Riociguat therapy will be initiated following washout periods of 24 and 48 hours for sildenafil and tadalafil, respectively. ERA treatment will be continued at the stable dose in both arms.

Results
The planned enrollment of REPLACE is 218 patients. The primary efficacy endpoint ‘satisfactory clinical response’ will be assessed at Week 24 and is defined as a composite fulfillment of 2 of the 3 parameters – ≥10% or ≥30 m increase from baseline in 6MWD; WHO FC I or II; and ≥30% reduction from baseline N-terminal prohormone of brain natriuretic peptide (NT-proBNP) – in the absence of clinical worsening. This will be reviewed and confirmed by an independent clinical endpoint committee. Secondary efficacy outcomes will comprise change from baseline in 6MWD (blinded assessment), NT-proBNP, WHO FC (blinded assessment), and clinical worsening. Exploratory analyses will include quality of life (Living with Pulmonary Hypertension questionnaire), modified REVEAL risk score, and cardiac magnetic resonance imaging of a subset of patients. Safety will be evaluated by adverse events and all-cause mortality.

Conclusion
The REPLACE study will evaluate whether it is clinically beneficial to switch patients with PAH who do not achieve or maintain treatment goals with PDE5i therapy to riociguat.

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Abstract Title
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

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