ONLINE SUPPLEMENARY APPENDIX

Patients

Patients with symptomatic PAH were included in PATENT-1 if they were aged 18–80 years, had a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg, a PVR of >300 dyn·s·cm^{-5} and a 6MWD of 150–450 m. Patients with pulmonary venous hypertension, indicated by baseline pulmonary capillary wedge pressure >15 mmHg if aged 18–75 years at Visit 1 or >12 mmHg if aged >75 years at Visit 1, were excluded (the 12 mmHg cut-off was not applicable to the PAH-CHD population, as all patients were 18–75 years at baseline). Patients who had received no prior PAH-specific therapies (treatment-naïve) and those who were receiving ERAs and/or non-intravenous prostanoids at stable doses for ≥90 days were eligible for inclusion. Patients receiving PDE-5 inhibitors were excluded.

Study design and procedures

PATENT-1 was a 12-week randomised, double-blind, placebo-controlled, Phase III trial in which eligible patients were randomly assigned in a 2:4:1 ratio to receive placebo, oral riociguat individually adjusted up to a maximum of 2.5 mg three times daily (tid) (2.5 mg–maximum group) or riociguat up to 1.5 mg tid (1.5 mg–maximum group; this group was exploratory and not included in efficacy analyses). Details of the riociguat dose-adjustment schedule used in PATENT-1 have been published previously.[1]

PATENT-2 is an open-label long-term extension study that includes patients who completed PATENT-1 without ongoing study drug-related serious adverse events (AEs). The study comprises an 8-week double-blind dose-adjustment period, followed by an open-label phase that will continue until all patients transition to commercially available riociguat (study ongoing at the time of writing). Patients in PATENT-2 received riociguat up to 2.5 mg tid; details of riociguat dose adjustment in PATENT-2 have been published previously.[2]

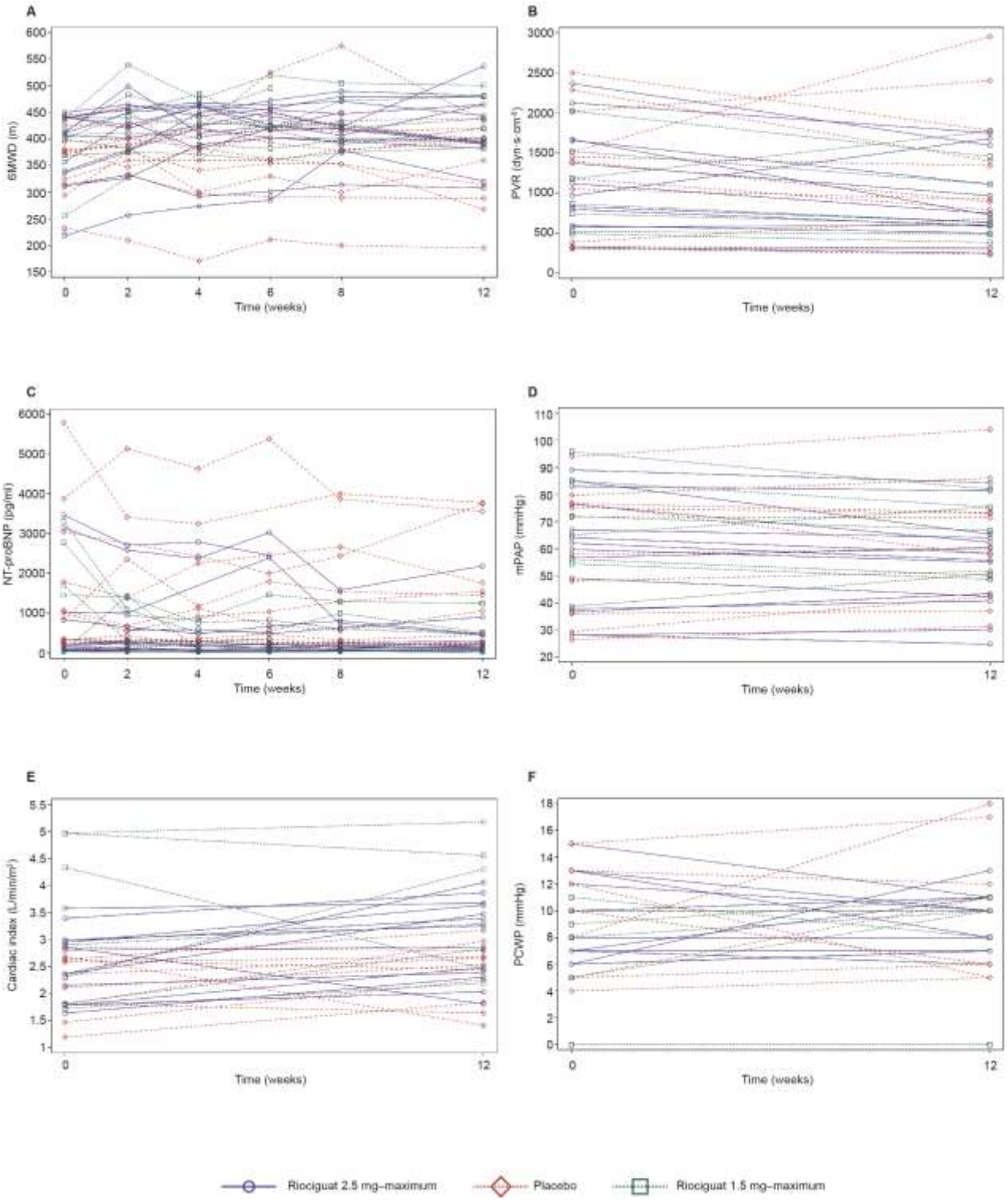
Outcome measures

The primary endpoint in PATENT-1 was change in 6MWD from baseline to end of Week 12. Secondary efficacy endpoints included change in PVR, NT-proBNP levels, WHO FC, time to clinical worsening, Borg dyspnoea score and quality of life scores (measured using the EuroQol Group 5-Dimensional Self-report Questionnaire and the Living with Pulmonary Hypertension questionnaire). Safety assessments included AEs and serious AEs, laboratory evaluations, and monitoring of vital signs and echocardiograms throughout the study and safety follow-up period. The primary aim of PATENT-2 was to assess the safety and tolerability of long-term riociguat. Exploratory efficacy assessments included 6MWD and WHO FC.

References

1. Ghofrani HA, Galiè N, Grimminger F, *et al*. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;369:330-40
2. 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

Supplementary figure 1 Changes in 6MWD (A), PVR (B), NT-proBNP (C), mPAP (D), cardiac index (E), and PCWP (F) in individual patients with PAH-CHD over the course of PATENT-1.



6MWD, 6-minute walking distance; CHD, congenital heart disease; mPAP, mean pulmonary artery pressure; NT-proBNP, *N*-terminal of the prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.