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Title: Effect of macitentan on morbidity and mortality in pulmonary arterial hypertension: A randomised controlled trial (SERAPHIN)

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Body: The effect of macitentan, a novel dual endothelin receptor antagonist, on morbidity and mortality was assessed in patients with pulmonary arterial hypertension (PAH). In this double-blind, placebo-controlled, Phase III, event-driven study (SERAPHIN; NCT00660179), 742 PAH patients (≥12 years) were randomised to placebo (n=250), macitentan 3mg (n=250) or 10mg (n=242) once daily. 64% received PAH-specific drugs at baseline. Mean treatment duration was 85.3, 99.5 and 103.9 weeks, respectively. The primary endpoint was time from treatment initiation to first morbidity or mortality event (death, atrial septostomy, lung transplantation, initiation of i.v./s.c. prostanoids or PAH worsening – blindly and independently adjudicated).

Macitentan reduced the risk of such an event vs placebo by 30% (97.5%CI: 4–48%; P=0.0108) in the 3mg group and 45% (97.5%CI: 24–61%; P<0.0001) in the 10mg group. This effect was established early, sustained over the entire study duration and, for the 10mg dose, was preserved across WHO functional class (FC), as well as in combination with other PAH-specific drugs. Macitentan 3mg and 10mg reduced the risk of PAH-related death or hospitalisation (a composite secondary endpoint) by 33% (97.5%CI: 3–54%; P=0.0146) and 50% (97.5%CI: 25–67%; P<0.0001). Macitentan was well tolerated; incidences of elevated liver aminotransferases and peripheral oedema were similar across groups. Headache, nasopharyngitis and anaemia occurred more frequently with macitentan than placebo. In conclusion, macitentan significantly reduced morbidity and mortality in patients with PAH, with a favourable safety profile.